

SELECT COMMITTEE ON
SCIENCE AND TECHNOLOGY

CANNABIS

THE SCIENTIFIC AND MEDICAL EVIDENCE

REPORT

Ordered to be printed 4 November 1998

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References to evidence

Q refers to a question in oral evidence; p refers to a page of written evidence. All the evidence is printed in a separate volume, HL Paper 151-I, Session 1997-98.

NINTH REPORT

4 November 1998

By the Select Committee appointed to consider Science and Technology.

ORDERED TO REPORT

CANNABIS: THE SCIENTIFIC AND MEDICAL EVIDENCE

CHAPTER 1 INTRODUCTION

1.1 Cannabis has been used medically for thousands of years in oriental and Middle Eastern countries and as an intoxicant for many hundreds of years in India and in the Middle East; and it was employed in Western medicine for at least two millennia. The medical use of cannabis in Europe and North America, however, declined in this century because of the lack of any standardised preparations of the plant product and its unreliable absorption when given by mouth, and because of the development of more potent and reliable drugs for the conditions for which cannabis was then being used.

1.2 During the 1960s and 1970s there was a large increase in the use of smoked cannabis as an intoxicant in the USA and in Europe, where it had been largely unknown previously as a drug of abuse. The recreational use of cannabis has continued to increase in recent years, particularly among the young. Medical use in the United Kingdom was prohibited in 1973; but cannabis is now the most widely used of all illegal intoxicants.

1.3 During the 1980s and 1990s there has been renewed interest in the potential medical uses of cannabis and its derivatives. Substantial numbers of patients with various conditions are illegally self-medicating with cannabis and are convinced that they derive medical benefit—although scientific evidence for or against such a conclusion is largely lacking. This has led to calls for cannabis again to be made available for medical applications.

1.4 In Britain this debate has led a number of expert bodies to review the medical and scientific evidence for and against such proposals. The British Medical Association published a report on the topic in 1997¹. The Department of Health recently commissioned three literature reviews on cannabis, at the request of the Advisory Council on the Misuse of Drugs (ACMD); we have seen these (they were placed in the Library of the House on 9 June), and the authors have all given evidence to this inquiry². Reports were also published last year by the US National Institutes of Health and the American Medical Association³.

1.5 In the light of this heightened interest in cannabis, and particularly the report by the BMA, we decided to examine the scientific and medical evidence to determine whether there was a case for relaxing some of the current restrictions on the medical uses of cannabis. We have also

¹ *Therapeutic uses of cannabis*, BMA/Harwood Academic Publishers, 1997, ISBN 90-5702-318-0.

² *Cannabis: clinical and pharmacological aspects*, by Prof C H Ashton; *Psychiatric aspects of cannabis use*, by Dr A Johns; *Therapeutic aspects of cannabis and cannabinoids*, by Dr P Robson.

³ NIH Report on the medical uses of marijuana, August 1997; AMA Medical Marijuana, December 1997.

considered whether the continued prohibition of recreational use is justified on the basis of the scientific evidence of adverse effects. Recreational use raises other issues besides the adverse effects of the drug; these are outside our remit "to consider science and technology", belonging instead to the realms of law, sociology and even philosophy, and we have not considered them. Neither have we considered whether cannabis is a stepping stone or gateway to other more dangerous drugs; we have confined our considerations solely to cannabis.

1.6 Chapters 2 and 3 of this Report are introductory, giving brief accounts of the history of cannabis and its pharmacology. In Chapters 4-7 we review the evidence which we have received on the four key issues: the adverse effects of taking cannabis; current and proposed medical uses; recreational use; and the implications of possible changes to the law. Our conclusions and recommendations are set out in Chapter 8.

1.7 This report was prepared by Sub-Committee I, whose members are listed in Appendix 1. They received evidence from the persons and organisations listed in Appendix 2, to all of whom we are grateful for their help. We are particularly grateful to the Sub-Committee's Specialist Adviser, Professor Leslie Iversen FRS, Visiting Professor of Pharmacology at the University of Oxford. Professor Iversen attended two international conferences on the Sub-Committee's behalf; his accounts of these appear in Appendices 3 and 4. Abbreviations are listed in Appendix 5.

1.8 We also acknowledge the assistance of the Parliamentary Office of Science and Technology (POST). POST's report *Common Illegal Drugs and their Effects* (May 1996), and POST note 113 *Cannabis Update* (March 1998), have been particularly helpful.

CHAPTER 2 HISTORY OF THE USE OF CANNABIS

2.1 The earliest known reference to cannabis is in Assyrian tablets of the seventh century BC. It has thus been in use for at least 2600 years. Like very many other herbs, it has been used medically for a wide variety of ailments, especially throughout Asia and the Middle East. The mild euphoria that it induces led to its use as an intoxicant, perhaps most notably in countries where Islam prohibited the use of alcohol.

2.2 In Western medicine, it appeared in the Herbal (i.e. pharmacopoeia) of Dioscorides of about 60 AD, and in all subsequent herbals. The 16th century saw a detailed interest in cannabis, with reports of it and its usages being sent back by many travellers to the East, and the number of possible uses given in the herbals doubled. In England, the Herbal of John Gerard (1597) recommended it as it "consumeth wind and drieth up seed [i.e. semen]", and quoted Dioscorides as recommending it for easing the pain of earache and for the treatment of jaundice. Nicholas Culpeper, in his Herbal (1653), gave the same indications for the use of cannabis seeds, and also recommended the decoction of the roots, as this "allayeth inflammations, easeth the pain of gout, tumours or knots of joints, pain of hips...".

2.3 In these and other early Herbals, each medicine was said to have multiple uses, often without justification. More critical views ultimately prevailed, but only slowly. Thus by 1788 the *New Edinburgh Dispensatory* still included three quarters of the entries of Dioscorides, but excluded most animal products. Such exotic remedies as "scrapings of an elephant's tooth", "dust from the walls of a wrestling school" and, remarkably, as a cure for quartan malaria, "seven bed bugs in meat and beans", had been eliminated. The loss of the animal products and most of the minerals left the 1788 *New Dispensatory* consisting mainly of herbal remedies. There was little change for 150 years, and the British Pharmacopoeia of 1914 included most of the contents of the volume of 1788. But the situation was about to change radically, with the rise of synthetic pharmaceutical chemistry.

2.4 Meanwhile, in 1833 Samuel Carey in his *Supplement to the Pharmacopoeia and Treatise on Pharmacology* advised that cannabis could be used to make "an agreeable intoxicating drink". This is the only British reference to cannabis as an intoxicant known to us from this period.

2.5 Cannabis was reintroduced into British medicine in 1842 by Dr W O'Shaughnessy, an army surgeon who had served in India. In Victorian times it was widely used for a variety of ailments, including muscle spasms, menstrual cramps, rheumatism, and the convulsions of tetanus, rabies and epilepsy; it was also used to promote uterine contractions in childbirth, and as a sedative to induce sleep. It is said to have been used by Queen Victoria against period pains: there is no actual proof of this at all, but Sir Robert Russell, for many years her personal physician, wrote extensively on cannabis, recommending it for use in dysmenorrhoea. It was administered by mouth, not by smoking, but usually in the form of a tincture (an extract in alcohol). Cannabis extracts were also incorporated in many different proprietary medicines.

2.6 "People were well aware at that stage that [cannabis] was an unpredictable drug" (Edwards Q 26). The advent of a host of new and better synthetic drugs led to the abandonment of many ancient herbal remedies, including cannabis. Thus in the British Pharmacopoeia of 1932 no fewer than 400 herbal remedies were omitted, among them cannabis, extract of cannabis and tincture of cannabis—though all three remained in the British Pharmaceutical Codex of 1949⁴.

2.7 Until 1968, the only control of medicines in the United Kingdom (other than those regarded as dangerous) was provided by the pharmacopoeias, which set quality standards for the preparation of drugs. The Medicines Act 1968 was enacted following the thalidomide tragedy: it

⁴ The British Pharmaceutical Codex, produced by the Royal Pharmaceutical Society of Great Britain, was a source of officially recognised standards for pharmaceutical preparations until 1979. Since then it has been in the process of being superseded by the British and European Pharmacopoeias.

gave the Government power to license pharmaceutical companies, and individual products and clinical trials. It also established the Medicines Commission and the Committee on the Safety of Medicines, to advise the Government on the exercise of their new powers. Existing drugs received "licences of right". The licensing powers are now exercised through the Medicines Control Agency (MCA). Doctors may prescribe an unlicensed drug, or a licensed drug for an unlicensed indication ("off-label"); but they do so at their own risk, and without the benefit of the surveillance for adverse effects which is conducted in respect of licensed medicines through the "yellow card" system.

2.8 Drug abuse has been the subject of international conventions since 1912. In 1961 these were consolidated and brought up to date by the UN Single Convention on Narcotic Drugs. Cannabis and cannabis resin were listed in Schedule IV, which entitled (but did not oblige) parties to adopt "special measures of control", and to ban them altogether "except for amounts which may be necessary for medical and scientific research only, including clinical trials..." (Article 2.5). According to the Home Office (p 150), this reflected "WHO's view that the drug was widely abused, had no therapeutic value and was obsolete in medical practice". Under the Dangerous Drugs Act 1964 (shortly consolidated by the Dangerous Drugs Act 1965), which implemented the Convention in the United Kingdom, cannabis was still able to be prescribed, though subject to certain controls. The tincture received a "licence of right" under the Medicines Act 1968; doctors were therefore still able to prescribe it.

2.9 The scale of drug abuse increased dramatically during the 1960s. In 1971 the UN adopted a further Convention on Psychotropic Substances; and the United Kingdom enacted the Misuse of Drugs Act 1971, which repealed the Act of 1965 and other enactments, replacing them with a more comprehensive and flexible regime. Cannabinol and its derivatives including THC (the chemical which gives cannabis its psychoactive properties—see Chapter 3) appeared in Schedule I to the Convention, and parties were therefore obliged to ban them "except for scientific and very limited medical purposes by duly authorized persons" (Article 7(a)). In 1973 the licences of right granted in 1968 were reviewed, and the original Misuse of Drugs Regulations (SI 1973 No. 797) were made under the 1971 Act. Cannabis's licence of right was not renewed, and the Regulations listed cannabis, cannabis resin and cannabinol and its derivatives in Schedule 4—which is now Schedule 1 to the Misuse of Drugs Regulations 1985 (No. 2066)—thereby prohibiting medical use altogether.

2.10 According to the MCA, by 1973 there was "insufficient evidence" to support medical use of the tincture (Q 174), and it was rarely prescribed except to patients who were already drug misusers. The Parliamentary Under-Secretary of State for Health told the Commons on 14 January 1998 (col. 320), "It was rarely used and, when it was, it was used mainly for its sedative qualities. Advice at the time from the World Health Organization was that cannabis was no more effective than any other available drug in treating the conditions for which it was used, so its use was stopped." According to the Department of Health, there was also a problem of diversion to recreational use through bogus prescriptions (Q 174).

CHAPTER 3 PHARMACOLOGY OF CANNABIS AND THE CANNABINOIDS

3.1 The plant *Cannabis sativa* is also known as hemp; it is related to the nettle and the hop. It grows readily in a warm climate, and may be grown in more temperate regions. As a drug of abuse, it usually takes the form of herbal cannabis (marijuana), consisting of the dried leaves and female flower heads, or cannabis resin (hashish), the resin secreted by the leaves and flower heads, which may be compressed into blocks.

3.2 The family of chemically related 21-carbon alkaloids found uniquely in the cannabis plant are known as cannabinoids. There are more than 60 different cannabinoids; one of these, Δ^9 -tetrahydrocannabinol (THC), is the most abundant and accounts for the intoxicating properties of cannabis. Other cannabinoids which occur in some abundance (e.g. cannabidiol and cannabinol) are not psychoactive, but it is thought that they may modify the effects of THC. The amounts and proportions of the various cannabinoids in each plant vary from strain to strain, and can be adjusted by breeding. By coincidence, the chemistry and pharmacology of cannabis were among the principal interests of the late Lord Todd, when he worked at Manchester University in the 1930s; he went on to become, among other things, the first Chairman of the House of Lords Select Committee on Science and Technology on its establishment in 1979.

3.3 THC and other cannabinoids dissolve readily in fat but not in water. This limits the possible formulations of cannabis and cannabinoid preparations, and slows down their absorption from the gut. On the other hand, when cannabis is smoked (in a "joint" or "reefer", or in a pipe), THC is absorbed very quickly into the bloodstream, through the large surface area of the pharynx and the lungs. After smoking, the psychoactive effects of THC are perceptible within seconds, and peak effects are achieved within minutes. When cannabis or cannabinoids are taken by mouth, peak effects may not occur for several hours, but they last longer. After smoking or oral ingestion, the drug persists in the brain longer than in the blood; so the psychological effects persist for some time after the level of THC in the blood has begun to decline.

3.4 Smoking delivers 30 per cent or more of the total THC in a cannabis cigarette to the blood stream. The proportion of THC absorbed after taking cannabis by mouth is 2–3 times less, because after absorption in the gut the drug is largely degraded by metabolism in the liver before it reaches the general circulation. Preliminary reports indicate that absorption into the circulation can be increased if THC is administered by rectal suppository, as this route delivers the drug directly into the circulation, avoiding the liver.

3.5 Once THC has entered the bloodstream, it is widely distributed in the body, especially in fatty tissues. The slow release of THC from these tissues produces low levels of drug in the blood for several days after a single dose, but there is little evidence that any significant pharmacological effects persist for more than 4–6 hours after smoking or 6–8 after oral ingestion. The persistence of the drug in the body, and the continuous excretion of degradation products in the urine, can however give rise to cannabis-positive forensic tests days or even weeks after the most recent dose. (The implications of this for roadside testing of drivers are considered below, at paragraph 4.9.)

3.6 According to Professor Trevor Robbins, speaking for the Medical Research Council (MRC), "Cannabinoid pharmacology has exploded in the last decade..., opening up...all sorts of exciting possibilities" (Q 628). These advances are reviewed in evidence to this Committee by the Royal Society and by Dr Roger Pertwee of the University of Aberdeen⁵. It is now recognised that THC interacts with a naturally occurring system in the body, known as the cannabinoid system. THC takes effect by acting upon cannabinoid receptors (see Box 1). Two types of cannabinoid receptor have been identified: the CB1 receptor and the CB2 receptor. CB1 receptors are present on nerve cells in the brain and spinal cord as well as in some peripheral tissues (i.e. tissues outside

⁵ Dr Pertwee is a world expert on the cannabinoids, and current President of the International Cannabinoid Research Society. At the University of Aberdeen, he heads a research team of eight scientists engaged in research in this area. He was a contributing author to the BMA report.

the brain); CB2 receptors are found mainly on cells of the immune system and are not present in the brain.

3.7 The roles played by CB1 and CB2 receptors in determining the various effects of cannabis in the whole organism remain to be established. Among the effects of cannabinoids known from animal experiments to be mediated by CB1 receptors are pain relief, impairments in memory and in the control of movements, lowering of body temperature and reductions in the activity of the gut. As CB1 receptors are the only ones known to exist in the brain, it is assumed that they mediate the intoxicant effects of THC. Little is known about the physiological role of the more recently discovered CB2 receptor, but it seems to be involved in the modulation of the function of the immune system.

BOX 1: CANNABIS PHARMACOLOGY—TERMINOLOGY

In common with many other drugs, the effects of THC result from its ability to activate special proteins known as *receptors* found on the surface of certain cells. The drug binds specifically to these proteins and activates a series of processes within the cells, leading to alterations in the cell's activity. Drugs, such as THC, that are able to "switch on" a receptor are known as *agonists* at that receptor. Other substances, however, bind to the receptor and, rather than activating it, prevent its activation by agonists; such substances are known as receptor *antagonists*.

The term *cannabinoid* was originally used to describe the family of naturally occurring chemicals found in cannabis, of which THC is the principal member. It is now also taken to encompass all those substances capable of activating cannabinoid receptors. These include the naturally occurring plant cannabinoids, certain synthetic substances (e.g. nabilone—see Box 4 below), and the recently discovered *endogenous cannabinoids* (see paragraph 3.8 below).

3.8 Another important recent discovery has been that the body contains naturally occurring ("endogenous") compounds that can activate cannabinoid receptors. The most important of these "endogenous cannabinoids" are the fat-like materials arichidonylethanolamide ("anandamide") and 2-arichidonyl-glycerol (2-AG).

3.9 These discoveries have transformed the character of scientific research on cannabis, from an attempt to understand the mode of action of a psychoactive drug to the investigation of a hitherto unrecognised physiological control system in the brain and other organs. Although the physiological significance of this system is still largely unknown, one of the principal actions of THC and the endogenous cannabinoids seems to be to regulate the amounts of chemical messenger substances released from nerves in the brain, thus modulating neural activity.

3.10 The discovery of the endogenous cannabinoid system has significant implications for future pharmaceutical research in this area. Drugs that selectively activate CB1 or CB2 receptors (agonists), or selectively block one or other of these receptor types (antagonists), have already been developed by some pharmaceutical companies (Lambert p 109 and Q 438; Pertwee Q 285). Agonists to the CB2 receptor may have beneficial effects in modulating immune responses, and would not be expected to possess any psychoactive properties as the CB2 receptor is not found in the brain. Antagonists to the CB1 receptor are also being investigated, as novel therapeutic agents with the potential of reducing memory deficits associated with ageing or neurological disease, as novel treatments for schizophrenia or other psychoses, and as appetite suppressants.

3.11 It seems likely that most of the putative medical indications proposed for cannabis involve actions of the drug on CB1 receptors in the central nervous system. Extensive attempts were made by academic and pharmaceutical industry researchers during the 1970s to develop new

chemically modified cannabinoid molecules that separated the desired therapeutic effects from the psychoactive properties of these substances; but so far no such compound has been discovered.

3.12 Research continues apace. Professor Patrick Wall of St Thomas' Hospital⁶ reports "intense activity in universities and pharmaceutical companies" in this field; "Large numbers of cannabinoids are being synthesised and investigated particularly by US companies" (p 31); "It is an exciting period" (Q 101, cp Q 125, Pertwee QQ 281–298 and Notcutt Q 411). According to Dr Lambert, "The pharmaceutical industry has now provided the researcher with a wide range of tools to probe the cannabinoid system"⁷.

3.13 Recent data from animal studies reveal that, in common with various drugs of addiction (heroin, cocaine, nicotine and amphetamines), THC activates the release of the chemical messenger dopamine in some regions of the brain of rats (Pertwee Q 311, Wall Q 126). This is considered important as this pattern of dopamine release is thought to be associated with the rewarding properties of these drugs and hence may be related to their ability to cause dependence.

3.14 Other recent scientific findings indicate a relationship between the cannabinoid system in the brain and the naturally occurring opioid system⁸. The ability of THC to trigger dopamine release in the rat brain is blocked by prior administration of naloxone, a drug that selectively blocks the actions of opiates in the brain. This suggests that some of the psychoactive effects of THC and other cannabinoids may be mediated indirectly through an ability to activate the opioid system (Pertwee Q 311). Recent studies have also shown that the administration of THC to animals enhances the pain-relieving effects of morphine and related opiates. Furthermore, administration of naloxone (the opiate-blocker) to animals previously treated repeatedly with a cannabinoid produced some physical withdrawal signs; conversely, administration of a cannabinoid antagonist to animals previously dependent on heroin elicited some (but not all) of the signs of opiate withdrawal (see Appendix 4, paragraph 8). On the other hand, although some of the actions of THC may involve activation of the opioid system, THC does not mimic morphine or heroin either in its effects on animals or in the subjective experience of human users.

3.15 This new information may or may not be relevant to the debate as to whether cannabis induces physical dependence. We discuss the degree to which cannabis may induce dependence in man below, in Chapter 4.

⁶ Professor Wall is editor-in-chief of the medical journal *Pain*; he was a contributing author to the BMA report, and appeared before us on behalf of the ACT.

⁷ Hirst R A, Lambert D G and Notcutt W G, *Pharmacology and potential therapeutic uses of cannabis*. Br. J. Anaesthesia, July 1998.

⁸ The opioid system consists of receptors normally activated by the enkephalins and endorphins, normally released in response to pain and stress. They are also activated by morphine, heroin and other opiates.

CHAPTER 4 TOXIC EFFECTS OF CANNABIS AND CANNABINOID: REVIEW OF THE EVIDENCE

4.1 The prohibition of the recreational use of cannabis, and some of the doubts about medical use, are based on the presumption that cannabis is harmful to individual and public health. We have tested the strength of that presumption, and this Chapter records what we have found. New research on this subject is constantly coming forward, so this cannot be said to be the last word on it. Although cannabis is not in the premier league of dangerous substances, new research tends to suggest that it may be more hazardous to health than might have been thought only a few years ago (Edwards QQ 21, 27).

4.2 In assessing the adverse effects associated with cannabis use, we have been assisted by a number of detailed recent reviews, including the recent WHO report *Cannabis: a health perspective and research agenda* (WHO/MSA/PSA/97.4); the Australian National Drug Strategy report *The health and psychological consequences of cannabis use* (1994) and other documents⁹ submitted by Professor Wayne Hall, Executive Director of the Australian National Drug and Alcohol Research Centre in Sydney, and his colleagues; and the recent reviews noted above commissioned by the Department of Health. The evidence submitted to us by the Royal Society and the Royal College of Psychiatrists is also particularly relevant.

Acute (short-term) effects of cannabis

4.3 The acute toxicity of cannabis and the cannabinoids is very low; no-one has ever died as a direct and immediate consequence of recreational or medical use (DH QQ 219-223). Official statistics record two deaths involving cannabis (and no other drug) in 1993, two in 1994 and one in 1995 (HC WA 533, 21 January 1998); but these were due to inhalation of vomit. Animal studies have shown a very large separation (by a factor of more than 10,000) between pharmacologically effective and lethal doses.

4.4 One minor toxic side-effect of taking cannabis which merits attention is the short-term effect on the heart and vascular system. This can lead to significant increases in heart rate and a lowering of the blood pressure (Pertwee Q 299). For this reason patients with a history of angina or other cardiovascular disease could be at risk and should probably be excluded from any clinical trials of cannabis-based medicines.

4.5 The most familiar short-term effect of cannabis is to give a "high" — a state of euphoric intoxication. This is, of course, precisely the effect sought by the recreational user, analogous to the effect of alcohol and sought for similar reasons. We have been told, however, that people who use cannabis for medical purposes regard it as an unwelcome side-effect (Hodges Q 97).

4.6 Intoxication with cannabis leads to a slight impairment of psychomotor and cognitive function, which is important for those driving a vehicle, flying an aircraft or operating machinery (DH Q 197). The Department of Health rate this as "the major concern from a public health perspective" raised by recreational use (p 46), and Professor Hall considers it the most serious possible short-term consequence of cannabis use, both for the user and for the public (p 222).

4.7 There is some disagreement about how long such impairments persist after taking cannabis: most assume that they last for only a few hours (e.g. Kendall p 266); but Professor Heather Ashton of the University of Newcastle-upon-Tyne, principal author of the BMA report, suggested that subtle cognitive impairments could persist for 24 or even 48 hours or more (Q 72), whereas the DETR say "probably 24 hours at most" (*Press Notice 94/Transport*, 11 February 1998). On the other hand the impairment in driving skills does not appear to be severe, even

⁹ Including Hall W, Room R and Bondy S, *A comparison of the health effects of alcohol, cannabis, tobacco and opiates*, in Kallant H, Corrigal W, Hall W and Smart R eds *The Health Effects of Cannabis*, Addiction Research Foundation, Toronto, 1998; and articles awaiting publication in *Addiction* (*Respiratory risks of cannabis smoking*, 1998, 93, 1461), *Drug and Alcohol Review*, and the *Lancet* Seminar series (14 November 1998).

immediately after taking cannabis, when subjects are tested in a driving simulator. This may be because people intoxicated by cannabis appear to compensate for their impairment by taking fewer risks and driving more slowly, whereas alcohol tends to encourage people to take greater risks and drive more aggressively (POST note 113; cp DH p 240).

4.8 Analysis of blood samples from road traffic fatalities in 1996–97 (the results of the first 15 months of a three year DETR study—*Press Notice 94/Transport*, 11 February 1998) showed that 8 per cent of the victims were positive for cannabis, including 10 per cent of the victims who were driving. However, it is not clear what figures would have been obtained from a random sample of road users not involved in accidents (DH Q 211); and some of those who tested positive may have taken the cannabis as much as 30 days before, so that the effects would have worn off long since (DH p 240). The interpretation of traffic accident data is further confounded by the fact that 22 per cent of the drivers found to be cannabis-positive also had evidence of alcohol intake; proportions of alcohol-positives among cannabis-positive drivers as high as 75 per cent have been reported in other countries in similar studies. Professor Hall considers cannabis's contribution to danger on the roads to be very small; in his view the major effect of cannabis use on driving may be in amplifying the impairments caused by alcohol (cp Keen Q 42). According to a survey of 1,333 regular cannabis users by the Independent Drug Monitoring Unit (IDMU) in 1994, users who drove reported a level of accidents no higher than the general population; those with the highest accident rates were more likely to be heavier poly-drug users.

4.9 It is difficult to see how cannabis intoxication could be monitored, if its use were permitted. There could be no equivalent of the breathalyser for alcohol, since small amounts of cannabis continue to be released from fat into the blood long after any short-term impairment has worn off (see paragraph 3.5 above).

4.10 A single dose of cannabis for an inexperienced user, or an over-dose for an habitual user, can sometimes induce a variety of intensely unpleasant psychic effects including anxiety, panic, paranoia and feelings of impending doom (BMA p 9, RCPsych p 282). These adverse reactions are sometimes referred to as a “whitey” as the subject may become unusually pallid (Montgomery Q 577). These effects usually persist for only a few hours.

4.11 In some instances cannabis use may lead to a longer-lasting toxic psychosis involving delusions and hallucinations that can be misdiagnosed as schizophrenic illness (Strang Q 239, van der Laan Q 512). This is transient and clears up within a few days on termination of drug use; but the habitual user risks developing a more persistent psychosis, and potentially serious consequences (such as action under the Mental Health Acts and complications resulting from the administration of powerful neuroleptic drugs) may follow if an erroneous diagnosis of schizophrenia is made. It is also well established that cannabis can exacerbate the symptoms of those already suffering from schizophrenic illness (Q 239) and may worsen the course of the illness; but there is little evidence that cannabis use can precipitate schizophrenia or other mental illness in those not already predisposed to it (RCPsych p 283).

4.12 These relatively rare adverse psychological effects of cannabis are not considered to represent a serious limitation on the potential medical use of the drug (Strang Q 244), save that patients suffering from schizophrenic illness or other psychoses should be excluded. However they do constitute an issue for public health. According to the Department of Health, cannabis contributes to the extra cost of acute psychiatric services imposed by drug misuse, though this cannot be separately costed (p 46; cp RCPsych p 282). The Royal College of Psychiatrists (p 284) believe that the proportion of users who experience acute adverse mental effects is “significant”.

Chronic (long-term) toxicity

4.13 Cannabis can have untoward long-term effects on cognitive performance, i.e. the performance of the brain, particularly in heavy users. These have been reviewed for us by the Royal College of Psychiatrists and the Royal Society. While users may show little or no impairment in simple tests of short-term memory, they show significant impairments in tasks that require more complex manipulation of learned material (so-called "executive" brain functions) (Edwards Q 21). There is some evidence that some impairment in complex cognitive function may persist even after cannabis use is discontinued¹⁰; but such residual deficits if present are small, and their presence controversial (van Amsterdam Q 494, Hall Q 741). Dr Jan van Amsterdam of the Netherlands National Institute of Public Health and the Environment, who has reviewed the literature on long-term cognitive effects of prolonged heavy use and kindly came to Westminster to tell us his findings, pointed out the practical difficulties of assessing possible residual effects (Q 487). These include the impossibility of obtaining pre-drug baseline values (i.e. measures of the cognitive functioning of the subject before their first use of cannabis), the difficulty of estimating the drug dose taken, the need for a lengthy "wash-out" period after termination of use to allow for the slow elimination of residual cannabis from the body, and the possibility of confusing long-term deficits with withdrawal effects. He felt that many of the published reports on this subject had not taken adequate account of these problems.

4.14 The occurrence of an "amotivational syndrome" in long-term heavy cannabis users, with loss of energy and the will to work, has been postulated. However it is now generally discounted (van Amsterdam Q 503); it is thought to represent nothing more than ongoing intoxication in frequent users of the drug (RCPsych p 283).

4.15 Animal experiments have shown that cannabinoids cause alterations in both male and female sexual hormones; but there is no evidence that cannabis adversely affects human fertility, or that it causes chromosomal or genetic damage (WHO report ch.7). The consumption of cannabis by pregnant women may, however, lead to significantly shorter gestation and lower birth-weight babies in mothers smoking cannabis six or more times a week (WHO report ch.8; DH p 47). These effects may be due to the inhalation of carbon monoxide in cannabis smoke, which lowers the ability of the blood to carry oxygen to the foetus, rather to any direct effect of cannabinoids. If so, they are comparable with the effects of smoking tobacco.

4.16 The NHS National Teratology [i.e. foetal abnormality] Information Service advise, "There are a few case reports of malformations following marijuana use in pregnancy. However, there is no conclusive evidence to suggest either an increase in the overall malformation rate or any specific pattern of malformations". Nevertheless, they warn: "We would not recommend the legalisation of cannabis because of the potential fetotoxicity that may occur if it is used in pregnancy" (p 280).

4.17 Most of our witnesses regard the consequences of smoking cannabis as the most important long-term risk associated with cannabis use¹¹. Cannabis smoke contains all of the toxic chemicals present in tobacco smoke (apart from nicotine), with greater concentrations of carcinogenic benzantracenes and benzpyrenes. It has been estimated (BMA p 11) that smoking a cannabis cigarette (containing only herbal cannabis) results in approximately a five-fold greater increase in carboxy-haemoglobin concentration¹², a three-fold greater increase in the amount of tar inhaled, and a retention in the respiratory tract of one third more tar, than smoking a tobacco cigarette. Cannabis resin, the most commonly used form of cannabis in the United Kingdom, is often smoked mixed with tobacco, thus adding the well-documented risks of exposure to tobacco smoke, while complicating the picture for the researcher.

¹⁰ N Solowij, *Cannabis and Cognitive Functioning*, Cambridge University Press, 1998.

¹¹ See in particular DH p 46; papers kindly supplied by Professor Donald Tashkin, University of California Los Angeles School of Medicine, and Professor Hall; and Appendix 3, paragraph 8.

¹² Carboxy-haemoglobin is formed by the action of carbon monoxide on haemoglobin in the blood. It interferes with the transport of oxygen around the body.

4.18 Regular cannabis smokers suffer from an increased incidence of respiratory disorders, including cough, bronchitis and asthma. Microscopic examination of the cells lining the airways of cannabis smokers has revealed the presence of an inflammatory response and some evidence for what may be pre-cancerous changes. There is as yet no epidemiological evidence for an increased risk of lung cancer (DH p 46, Q 205); but, by analogy with tobacco smoking, such a link may take 25–30 years or more before it becomes evident, and the widespread use of smoked cannabis in Western societies dates only from the 1970s. There are some reports of an increased incidence of cancers of the mouth and throat in young cannabis users¹³, but so far these involve only small numbers and no cause and effect relationship has been established. Nevertheless, Professor Hall considers it a “pretty reasonable bet” that heavy users incur a risk of cancer (Q 741); and the risk is considered by some of our witnesses to be sufficiently serious to rule out any approval of long-term medical use of smoked cannabis, and to justify the present prohibition on recreational use.

Tolerance to cannabis

4.19 Tolerance is the phenomenon whereby a regular user of a drug requires more each time to achieve the same effect. It is not an adverse effect in itself; but it may make medical use more difficult, and recreational use more damaging as the user’s demand for the drug increases.

4.20 Dr Pertwee told us that both animal and human data show that tolerance can develop on repeated administration of high doses of cannabinoids; tolerance may develop more readily to some effects in animals (e.g. lowering of body temperature) than to others (Q 304). However Clare Hodges¹⁴, a sufferer from MS, said that she had not experienced tolerance to the palliative effects of low doses of cannabis, and had been taking the same dose (9g of herbal cannabis per week, costing about £30 per week, usually smoked) for six years; neither had other medical users reported tolerance in their experience (QQ 117–119; cp LMMSG p 269).

4.21 Whether tolerance develops may therefore depend on how much drug is consumed, and how often. Neil Montgomery, a research journalist currently studying cannabis users through the Department of Social Anthropology at the University of Edinburgh, said that his observations of heavy cannabis users (using more than 28g of cannabis resin per week) suggested that they needed as much as eight times higher doses to achieve the same psychoactive effects as regular users consuming smaller doses of the drug (Q 570). Clear evidence of tolerance has also been reported in volunteers given large doses of THC under laboratory conditions (Pertwee Q 304).

4.22 This conforms with the evidence of Professor Wall, who compared the experience with morphine and related opiate pain-relieving agents during the past 20–30 years, pioneered by Dame Cicely Saunders and the Hospice movement. This has shown that tolerance (and addiction—see below) are not major problems in the medical use of these drugs, although in recreational use they may pose severe problems (Q 120).

Dependence on cannabis

4.23 The repeated use of cannabis or cannabinoids does not result in severe physical withdrawal symptoms when the drug is withdrawn; so many have argued that these drugs are not capable of inducing dependence. Dr Pertwee, and Dr David Kendall of the University of Nottingham (p 267), however, described new evidence from animal studies showing marked signs of withdrawal in animals treated repeatedly with large doses of cannabinoids and then challenged with a newly developed cannabinoid CB1 receptor antagonist (see Box 1) called SR141716A. This has provided the first real evidence for physical dependence and withdrawal symptoms in animals (QQ 308–310).

4.24 The BMA report says that withdrawal symptoms from cannabis in man are mild and short-lived; but in the light of the newer definitions of dependence noted in Box 2 this evidence is

¹³ E.g. Taylor FM III, *Marijuana as a potential respiratory carcinogen: a retrospective analysis of a community hospital population*, South. Med. J. 1988, 81, 1213.

¹⁴ Miss Hodges is the founder-Director of the UK Alliance for Cannabis Therapeutics (ACT). “Clare Hodges” is a *nom de guerre*.

inconclusive. Professor Ashton indicated that she felt cannabis to be potentially addictive, and compared the withdrawal symptoms—tremor, restlessness and insomnia—to those experienced by users of alcohol, sleeping pills or tranquillisers. She had talked to students with quite severe cannabis withdrawal problems (Q 73).

BOX 2: DEFINITIONS OF DEPENDENCE

The consumption of any psychoactive drug, legal or illegal, can be thought of as comprising three stages: use, abuse, and addiction. Each stage is marked by higher levels of drug use and increasingly serious consequences.

Abuse and addiction have been defined and redefined by various organisations over the years. The most influential current system of diagnosis is that published by the American Psychiatric Association (DSM-IV, 1994). This uses the term *substance dependence* instead of addiction, and defines this as a cluster of symptoms indicating that the individual continues to use the substance despite significant substance-related problems. The symptoms may include *tolerance* (the need to take larger and larger doses of the substance to achieve the desired effect), and *physical dependence* (an altered physical state induced by the substance which produces physical *withdrawal symptoms*, such as nausea, vomiting, seizures and headache, when substance use is terminated); but neither of these is necessary or sufficient for the diagnosis of substance dependence. Using DSM-IV, dependence can be defined in some instances entirely in terms of *psychological dependence*; this differs from earlier thinking on these concepts, which tended to equate addiction with physical dependence.

The DSM-IV system also defines *substance abuse* as a less severe diagnosis, involving a pattern of repeated drug use with adverse consequences but falling short of the criteria for substance dependence.

4.25 Professor Griffith Edwards, a member of the Advisory Council on the Misuse of Drugs¹⁵ (Q 27), said that, using internationally agreed criteria (DSM-IV—see Box 2), there seemed no doubt that some regular cannabis users become dependent, and that they suffer withdrawal symptoms on terminating drug use. According to the WHO report, cannabis dependence is characterised by a loss of control over drug use, cognitive and motivational impairments that interfere with work performance, lowered self-esteem and often depression. Professor Hall wrote, “By popular repute, cannabis is not a drug of dependence because it does not have a clearly defined withdrawal syndrome. There is, however, little doubt that some users who want to stop or cut down their cannabis use find it very difficult to do so, and continue to use cannabis despite the adverse effects that it has on their lives.” In oral evidence he added that users who sought treatment for cannabis dependence had typically taken large amounts of cannabis every day for perhaps 15 years or more (Q 745).

4.26 The Institute for the Study of Drug Dependence likewise conclude that, while physical dependence is rare, “Regular users can come to feel a psychological need for the drug or may rely on it as a “social lubricant”: it is not unknown for people to use cannabis so frequently that they are almost constantly under the influence” (p 263).

4.27 One measure of the significance of cannabis dependence is the proportion of users who become dependent. Since cannabis dependence is poorly defined, and the total number of users is unknown, this figure is elusive. Data from a recent study of 200 regular users in Australia¹⁶ suggest that more than 50 per cent of such users may be classified as dependent, although many of

¹⁵ Professor Edwards is Professor Emeritus of Addiction Behaviour at the Institute of Psychiatry, University of London; past Chairman of the National Addiction Centre; and editor-in-chief of the journal *Addiction*. The ACMD is established under the Misuse of Drugs Act 1971, to advise the Government.

¹⁶ By Dr Wendy Swift, Australian National Drug and Alcohol Research Centre.

these do not consider themselves as dependent. This corresponds with the finding of an American study of 1991, cited by the WHO report, that "about half of those who use cannabis daily will become dependent". According to Professor Hall, "Epidemiological studies suggest that cannabis dependence in the sense of impaired control over use is the most common form of drug dependence after tobacco and alcohol, affecting as many as one in ten of those who ever use the drug" (p 221).

4.28 Neil Montgomery estimates that approximately 5 per cent of regular cannabis users are heavy users, consuming as much as 28g of cannabis resin per week. "These are people who have become dependent on cannabis; they are psychologically addicted to the almost constant consumption of cannabis...Becoming stoned and remaining stoned throughout the day is their prime directive" (Q 554).

4.29 Another measure of the extent of cannabis dependence is the number of people who seek treatment for it. Department of Health figures (1996) show that in 6 per cent of all contacts with regional drug clinics cannabis was the main drug of misuse (Q 27). A similar figure, that cannabis users constitute 7 per cent of all new admissions to drug treatment centres in Australia, was reported recently. Dr Philip Robson¹⁷, who runs a Regional Drug Dependence Unit in Oxford, said that 4.9 per cent of those admitted to his unit cited cannabis as their main drug (Q 462). However he did not regard cannabis as an important drug of addiction: "The drug falls well below the threshold of what would be expected for a dependency-producing drug which has clinical significance...I do not meet people who are prepared to knock over old ladies in the street or burglarise houses or commit other crimes to obtain cannabis". Professor Robbins estimated that at least 2 per cent of regular cannabis users (whom he defined as those using cannabis more than once a week) in the USA are dependent, on the basis of an estimate of 5m users and an official figure of 100,000 on specific treatment for cannabis dependency syndrome (Q 623).

4.30 It has been suggested that US figures may be inflated by people on compulsory treatment, for instance after testing positive at work, who may not in fact be dependent. According to Professor Hall, however, "In Australia ... drug testing is uncommon and there is no cannabis treatment industry. Yet treatment services...have seen an increase in the number of persons seeking help for cannabis" (p 221). He even suggests that the figures may be kept down by the widespread belief that it is not possible to be dependent on cannabis (Q 748).

4.31 Giving up cannabis is widely believed to be relatively easy: according to the Department of Health, "studies report that of those who had ever been daily users only 15 per cent persisted with daily use in their late twenties" (p 45). Most epidemiological studies in Britain and the United States have shown that the illicit use of cannabis mainly involves people in their late teens and twenties, with relatively few users over the age of 30.

4.32 It has been assumed that young cannabis users give up the habit when they enter their thirties; IDMU (p 236), however, suggest that this pattern may be changing. The British Crime Survey (1996) shows that although the prevalence of cannabis use falls after the age of 30, the greatest proportional increases in the period 1991–1996 were in older age groups, with incidence of past use doubling in the 40–44 age group (from 15 per cent to 30 per cent) and trebling in the 45–59 age group (from 3 per cent to 10 per cent). IDMU conclude that the current relatively low levels of cannabis use in the over-30 age group may reflect a generational and cultural divide, rather than substantial numbers of users giving up.

4.33 It is therefore clear that cannabis causes psychological dependence in some users, and may cause physical dependence in a few. The Department of Health sum up the position thus (p 45, cp Edwards Q 28): "Cannabis is a weakly addictive drug but does induce dependence in a significant minority of regular cannabis users."

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Consultant psychiatrist, Warneford Hospital; senior clinical lecturer, University of Oxford; author of one of the reviews for the Department of Health referred to in paragraph 1.4.

CHAPTER 5 MEDICAL USE OF CANNABIS AND CANNABINOIDS: REVIEW OF THE EVIDENCE

5.1 The main reason for our inquiry is that there are now calls for the law to be changed to permit wider medical use of cannabinoids, and to permit the medical use of cannabis itself. This Chapter reviews the evidence which we have received about current and proposed medical uses for cannabis and the cannabinoids. It is important to distinguish the different substances and preparations; for instance, cannabis leaf must be distinguished from cannabis extract, and whole cannabis from THC. It is also important, though not always easy, to distinguish the various possible routes of administration, e.g. by smoking and by mouth.

Current medical use of cannabis

5.2 Today in the United Kingdom, medical use of cannabis itself is illegal (see Box 3) but quite widespread. According to the BMA report, “many normally law-abiding citizens—probably many thousands in the developed world” use cannabis illegally for therapy. Most such users smoke their cannabis, but some take it by mouth. The UK Alliance for Cannabis Therapeutics (ACT) know of 200 people in the United Kingdom who have used cannabis for MS (p 29); 53 took part in a recent study of perceived effects of smoked cannabis¹⁸ (Q 262). Clare Hodges writes, “It is impossible to know how many people with MS use cannabis...My impression is that most people with MS do not”. A Multiple Sclerosis Society survey produced a figure of one per cent; but the Society believe the true figure to be higher (Q 341).

5.3 The ACT also know of 50 users with spinal injury, and 20 with other conditions. A survey conducted by the newspaper *Disability Now* in 1997 among its disabled readers revealed, among 200 respondents, 40 people taking cannabis for MS, 40 for spinal injury, 35 for back pain, 27 for arthritis and 64 for other conditions. IDMU’s surveys of 2,794 regular cannabis users have revealed 78 whose main reason for using it is medical (p 244).

5.4 We have received written evidence (not included in the volume of printed evidence) from four patients suffering from MS (besides Miss Hodges) who report that cannabis has a beneficial effect on their symptoms and call for a change in the law to permit the prescription of cannabis. Dr Fred Schon, a consultant neurologist, described the apparently dramatic improvement obtained by self-medication with smoked cannabis resin by an MS patient who had developed a severe and disabling abnormality of eye movements (p 303). We have also heard from people who have used cannabis against epilepsy, ME and pain, and as an anti-emetic after chemotherapy. Further anecdotal evidence was provided by the Alliance for Cannabis Therapeutics and the London Medical Marijuana Support Group.

5.5 According to Neil Montgomery, some users of cannabis for medical purposes are also, or have been, recreational users, and their medical use is to some extent conditioned by their recreational experience (p 132). Three of the nine such users who have given us evidence are in this category. An increasing number are growing their own cannabis, “primarily to avoid problems of impurity”, or buying in bulk to ensure consistency of dose; either course exposes them to stiffer sentences, if caught, than the frequent purchase of small quantities (cp IDMU p 261). Medical users typically take cannabis as frequently as, but in smaller quantities than, recreational users (Q 567).

5.6 Use of cannabis for medical purposes is sometimes connived at by the medical professions. Clare Hodges took medical advice before trying cannabis for her MS, and was not dissuaded (p 27). “Over 50 patients have told the ACT that their doctors have recommended that they try cannabis for symptomatic relief” (p 29); and 50 of the 200 respondents to the *Disability Now* survey said their doctor knew and approved. 100 doctors are associated with the ACT (Q 96).

¹⁸ Consroe P, Musty R, Rein J, Tillery W and Pertwee R, *The perceived effects of smoked cannabis on patients with MS*, Eur. Neurol. 1997, 38, 44.

BOX 3: CURRENT LEGAL CONTROLS

The regulation of cannabis in the United Kingdom under the Misuse of Drugs Act 1971 is complicated. Schedule 2 to the Act classifies cannabis itself, and cannabis resin, as Class B controlled drugs, and the cannabinoid cannabinal and its derivatives (defined as THC and 3-alkyl homologues thereof) as Class A controlled drugs. Offences involving Class A drugs attract stiffer penalties. Under the Act it is an offence to import, export, produce, supply or possess controlled drugs (though it is not an offence to use them); it is also an offence to cultivate cannabis plants, or to permit premises to be used for smoking cannabis.

Reference is often made in this context to "Schedule 1 and Schedule 2". These are Schedules not to the Act itself, but to the Misuse of Drugs Regulations 1985 (No. 2066) made under the Act. Schedules 2–5 list drugs to which various exemptions from the Act apply; in particular, drugs in Schedule 2 may be administered by, or on the instructions of, a doctor or dentist (Regulation 7), may be produced by a practitioner or pharmacist (Reg. 8), may be supplied (Reg. 8) and possessed (Reg. 10) by various classes of person, including practitioners, pharmacists and heads of laboratories, and may be possessed by patients (Reg. 10). Schedule 1 lists drugs to which the exemptions do not apply; cannabis, cannabis resin, and cannabinal and its derivatives (other than dronabinol—see Box 5) appear in Schedule 1.

The 1985 Regulations also empower the Secretary of State to license anyone to produce, possess or supply any controlled drug, including a Schedule 1 drug (Reg. 5); to license cultivation of cannabis plants (Reg. 12); and to approve premises for smoking cannabis for research purposes (Reg. 13).

The position in practice is therefore that cannabis and most of its derivatives may not be used in medicine, and may be possessed for research only under Home Office licence. There are two psychoactive cannabinoids, nabilone and dronabinol, which may be used for medicine: see Boxes 4 and 5. Two non-psychoactive cannabinoids, cannabidiol and cannabichromene, are not controlled drugs, and could in theory be prescribed as unlicensed medicines, but no-one is currently doing so.

This UK regime is one of the most restrictive in the world. Places with a more liberal regime include the Netherlands, Italy, Spain, Canada, and some states of Germany, Australia and the USA.

Most medical users tell the Multiple Sclerosis Society that their doctors are "mildly supportive" (Q 341). One user's doctor knows that she uses cannabis for pain relief and is unconcerned. Another took to cannabis for his epilepsy on a doctor's recommendation. On the other hand, a third user's consultant would not support his letter to us, "due to the advances in anti-emetic drugs". According to Dr William Notcutt, a consultant anaesthetist¹⁹, self-medication with cannabis for pain is now common, and "Advising on its use can be part of the pharmacological management of pain nowadays" (p 101, Q 434). Finally, the BMA report on medical use was itself prompted by a resolution in favour of medical use of "certain additional cannabinoids", passed by the BMA's Annual Representative Meeting in 1997.

5.7 The Government consider that the burden of proof rests on the proponents of medical use of herbal cannabis. As recently as 1 March 1994, the then Home Office Minister referred in a Commons answer to "long-standing advice that cannabis has no recognised medical use" (HC WA 632). Since then, the Government line appears to have softened a little: on 2 July 1997,

¹⁹ Dr Notcutt is a consultant in anaesthesia and pain management at James Paget Hospital, Great Yarmouth, and a senior lecturer at the University of East Anglia. He has extensive experience of the clinical use of nabilone (see Box 4) for the unlicensed indication of pain control.

Tessa Jowell MP, the Minister of State for Health, said that officials were keeping available research under review. "At present the evidence is inconclusive. The key point is that a cannabis-based medicine has not been scientifically demonstrated to be safe, efficacious and of suitable quality" (HC WA 174). On 27 October 1997, Paul Flynn MP put it to George Howarth MP, Under-Secretary of State at the Home Office, that cannabis was already widely used, illegally, by sufferers from MS, cerebral palsy and glaucoma; the Minister replied, "All drugs used for medical purposes have to be scientifically tested. If cannabis succeeds in those tests...the Secretary of State for Health...would be willing to consider allowing medicinal use of it. Unfortunately, as of now, there is no such evidence" (col. 580; see also HL 20 April 1998, WA 192, and HC 5 May 1998, WA 351).

5.8 The Department of Health say the same in written evidence: "There is insufficient evidence to demonstrate the effectiveness of cannabis as a therapeutic agent at this stage" (p 48). In oral evidence they went a little further: "We very much recognise the importance of research in this area and its potential value, particularly when addressed to the needs of patients for whom we have relatively little else to offer" (Q 167). But MS is not the only condition where conventional treatments are relatively limited in their effects, and the Department warned against allowing the "added frisson" of cannabis to distort the perspective (Q 225).

Advice to medical users

5.9 Given that use of cannabis for medical purposes is clearly going on in spite of the law, we asked some of our witnesses what advice they would give to people conducting or contemplating medical use, and to their doctors. The Department of Health suggest that doctors should advise users as to the legal position, and as to the "limited evidence" of efficacy. However, "one has also to recognise that people may choose to do things that their doctors advise against, and there would be a necessity for the doctor subsequently to continue to work to support that individual" (Q 172). One official went so far as to say, off the cuff but not off the record, "Other people's decisions have to be other people's decisions" (Q 224).

5.10 The BMA advise users of cannabis for medical purposes to be aware of the risks, to enrol for clinical trials, and to talk to their doctors about new alternative treatments; but they do not advise them to stop (Q 55). The Multiple Sclerosis Society "does not actually condone or encourage individuals in breaking the law" (Q 341).

Current medical uses of cannabinoids

5.11 Although cannabis itself is illegal, certain cannabinoids are in current use in UK medicine, within the law. Cannabinoids have anti-nausea effects, and have been used clinically to suppress the nausea and vomiting associated with chemotherapy in cancer patients. This is the only medical indication for which adequate data from controlled clinical trials exist, mostly from studies in the 1970s with pure THC and the synthetic cannabinoid nabilone, an analogue of THC, which were found to be as effective as prochlorperazine and other anti-nausea agents available at the time. On the basis of this evidence nabilone was licensed and is available as a prescription medicine in the United Kingdom for this indication (see Box 4). However, according to Professor Malcolm Lader of the Institute of Psychiatry, University of London²⁰ (Q 7), it has been little used. He believes that this is largely due to the fact that more powerful anti-nausea medicines were introduced in the 1980s—the serotonin antagonists ondansetron (Zofran), granisetron (Kytril) and tropisetron (Navoban), which are now widely used in conjunction with cancer chemotherapy (cp Hall p 221 and Appendix 3 paragraph 13). They have the advantage over the water-insoluble cannabinoids that they can be delivered intravenously as well as by mouth, and they are effective in up to 90 per cent of patients. There have been no clinical trials to compare the effectiveness of cannabinoids with the serotonin antagonists (RPharmSoc p 287).

²⁰ Chairman of the Technical Sub-Committee of the ACMD.

Box 4: NABILONE

Nabilone is an analogue of Δ^9 -THC. It was licensed in 1982 for prescription-only hospital-only use against nausea arising from chemotherapy and unresponsive to other treatment. It is manufactured synthetically by Eli Lilly & Co. Ltd and sold in the United Kingdom by Cambridge Selfcare Diagnostics Ltd; a pack of 20 1mg capsules (to be taken by mouth) costs £102. 5,400 packs were sold in 1997–98. It is not a controlled drug.

According to Dr Kendall of the University of Nottingham, nabilone is not widely used to treat nausea (p 268). Nabilone is used “very infrequently” in MS—probably less than cannabis itself (MSSoc Q 353). However Dr Notcutt is using it for pain control at James Paget Hospital in Great Yarmouth—see paragraph 5.14.

5.12 This means that cannabis and cannabinoids are likely to be of benefit as anti-emetics only to the small proportion of patients who do not respond to existing treatments, or possibly in the treatment of the delayed stages of emesis which can occur for some days following cancer chemotherapy, and which do not respond well to the serotonin antagonists. Nevertheless, cannabinoids are undoubtedly effective as anti-emetics and more research in this field might explore their use in combination with the serotonin antagonists, help to determine for which patients they are most appropriate, and examine the potential of the allegedly less psychoactive cannabinoid Δ^8 -THC, for which there have been encouraging preliminary clinical results (Q 74).

5.13 THC itself (dronabinol—see Box 5) is licensed as an anti-emetic in the USA, but not in this country. The BMA report recommends that it should be licensed here. This would depend on the manufacturer applying for a licence; in the mean time, doctors may prescribe it on an unlicensed basis at their own risk.

BOX 5: DRONABINOL

Dronabinol is THC. It is marketed as Marinol, synthetic Δ^9 -THC in sesame oil, supplied in soft gelatine capsules (to be taken by mouth) containing 2.5, 5 or 10mg of THC. It is licensed in the USA as an anti-emetic, and also to stimulate the appetite of AIDS patients. Marinol is manufactured by Unimed Pharmaceuticals Inc. in the USA; it is significantly more expensive than nabilone (Notcutt Q 427). It is not licensed as an anti-emetic here; but in 1995, on WHO advice, it was moved from Schedule 1 to Schedule 2 of the 1985 Regulations (by the Misuse of Drugs (Amendment) Regulations 1995, No. 2048), and may therefore be prescribed on the named-patient basis defined in the 1985 Regulations (see Box 6).

In a 1997 survey in the USA, only 6 per cent of 1,500 oncologists said they had prescribed dronabinol in the previous year (Brett p 204, cp Hall p 222). According to the BMA, take-up in the United Kingdom is low, because of the administrative obstacles and the availability of good alternatives (Q 83). According to Dr Notcutt of James Paget Hospital, Great Yarmouth (Q 422), it is not in practice available in the United Kingdom at present.

5.14 Dr Notcutt is currently treating patients suffering from intractable pain with nabilone, on an unlicensed basis. He has treated a total of 60 patients with a variety of chronic pain conditions, including MS, cancer, peripheral nerve damage and spinal lesions. As many as 50 per cent have derived some pain relief from nabilone, but a significant number of patients are unable to tolerate the side effects of the drug (unpleasant psychoactive effects and drowsiness) (Q 400) and the overall success rate is about 30 per cent (p 104).

5.15 Cannabis has been advocated to treat anorexia, but the scientific basis of this remains unclear. In normal subjects cannabis intake is followed about three hours later by an increased appetite ("the munchies"), particularly for sweet foods (Pertwee Q 256). Regular users of cannabis, however, become tolerant to this effect and appetite may even be depressed. According to the BMA report clinical trials have failed to establish any beneficial effect of THC on appetite in patients with anorexia nervosa. However, in controlled clinical trials in patients with advanced AIDS-related illnesses, dronabinol significantly reduced nausea, prevented further weight loss and improved patients' mood. On the basis of such data the US Food and Drug Administration have licensed dronabinol for the treatment of anorexia associated with AIDS; Dr Robson sees this as "the most compelling indication" for cannabis-based medicines (Q 458).

5.16 There is a concern with regard to the use of cannabinoids in AIDS because of the possible immunosuppressive effects of these drugs (BMA QQ 79, 80, Hall Q 742). Such effects could be damaging in patients whose immune system is already compromised, although there is no evidence of any relationship between cannabis use and the rate of progression to AIDS in HIV-positive men (Robson Q 460).

5.17 The BMA report recommends that the licensed indications for nabilone be extended to preventing weight loss and treating anorexia in patients with cancer or AIDS, and that dronabinol should be licensed in this country for this indication. As noted already, this would depend on application by the manufacturers; in the mean time, doctors may prescribe "off-label" at their own risk. Dronabinol is a controlled drug, listed in Schedule 2 to the Misuse of Drugs Regulations (see Box 2); so prescription would have to be on the "named-patient" basis defined in the Regulations (see Box 6).

BOX 6: PRESCRIPTION ON THE NAMED-PATIENT BASIS

Under Regulation 15 of the Misuse of Drugs Regulations 1985, any prescription for a drug listed in Schedule 2 (or Schedule 3) to the Regulations shall:

- " (a) be in ink or otherwise so as to be indelible and be signed by the person issuing it with his usual signature and dated by him;
- (b) insofar as it specifies the information required by sub-paragraphs (e) and (f) below to be specified, be written by the person issuing it in his own handwriting;
- (c) except in the case of a health prescription, specify the address of the person issuing it;
- (d) have written thereon, if issued by a dentist, the words "for dental treatment only" and, if issued by a veterinary surgeon or a veterinary practitioner, a declaration that the controlled drug is prescribed for an animal or herd under his care;
- (e) specify the name and address of the person for whose treatment it is issued or, if it is issued by a veterinary surgeon or veterinary practitioner, of the person to whom the controlled drug prescribed is to be delivered;
- (f) specify the dose to be taken and—
 - (i) in the case of a prescription containing a controlled drug which is a preparation, the form and, where appropriate, the strength of the preparation, and either the total quantity (in both words and figures) of the preparation or the number (in both words and figures) of dosage units, as appropriate, to be supplied;
 - (ii) in any other case, the total quantity (in both words and figures) of the controlled drug to be supplied;
- (g) in the case of a prescription for a total quantity intended to be supplied by instalments, contain a direction specifying the amount of the instalments of the total amount which may be supplied and the intervals to be observed when supplying."

Proposed new indications for cannabis-based medicines

5.18 Besides those conditions noted above for which cannabinoids are already used within the law, the conditions most often cited are MS and pain. Claims are also made in connection with epilepsy, glaucoma and asthma. We review the evidence on each of these conditions below.

Multiple sclerosis

5.19 The Multiple Sclerosis Society has in its membership 35,000 of the total of 85,000 patients suffering from this disease in the United Kingdom. The Society estimate that more than 1 per cent of these patients, and possibly as many as 3–4 per cent, are illegally using cannabis for relief of symptoms (Q 341). Representatives of the Society described for us the commonest symptoms of the disease. Fatigue is the most frequent in 95 per cent of patients, followed by balance problems (84 per cent), muscle weakness (81 per cent), incontinence (76 per cent), muscle spasms (66 per cent), pain (61 per cent) and tremor (35 per cent) (Q 334). Although the interferons (alpha and beta) are proving to be of some value in relapsing–remitting and progressive cases of the disease, these symptoms are still poorly controlled by existing treatments, and no cure has been found.

5.20 Dr Lorna Layward of the Multiple Sclerosis Society, and Dr Pertwee, reviewed for us the six published clinical trials of cannabis or cannabinoids in MS. These have involved small numbers of patients (a total of 41 subjects world-wide), but some positive results have been reported, especially for spasticity, pain associated with spasticity, tremor and urinary bladder control (QQ 262, 372). Dr Pertwee took part in the study of perceived effects of cannabis on MS noted above: in a postal survey of 112 MS patients self-medicating with cannabis in the United Kingdom and the USA, more than 90 per cent reported a beneficial effect on spasticity, and many also reported pain relief and improved urinary control (Q 262).

5.21 Dr Layward and Dr Pertwee referred to experimental results in animals which offer a scientific basis for the use of cannabis and cannabinoids in the treatment of MS. In an MS-like disease in mice (experimental autoimmune encephalomyelitis), low doses of cannabinoids alleviate the muscle tremor seen in such animals. Cannabinoids also suppress spinal cord reflexes in animals (QQ 262, 356).

5.22 It is natural to wonder whether the beneficial effects of cannabis reported by MS patients might simply be related to the feeling of well-being caused by the intoxicant properties of the drug. Clare Hodges said that cannabis greatly helped her physical symptoms, specifically the relief of discomfort in bladder and spine, and relief from nausea and tremors (Q 98). “Cannabis helps my body relax. I function and move much easier. The physical effects are very clear. It is not just a vague feeling of well-being”. She positively prefers to avoid intoxication, and feels able to control the dose of cannabis to obtain physical relief without getting high (p 27, Q 98; cp LMMSG p 270). Professor Wall likened this to the experience of patients using self-administered morphine or related narcotics for pain control, who control the dose to achieve a bearable level of pain without muddled thinking (Q 98).

5.23 The BMA report concluded, “It is somewhat paradoxical that cannabinoids are reported to be of therapeutic value in neurological disorders...since very similar symptoms can be caused by cannabis itself...it is not clear how much of the reputed effects of cannabis in motor disorders are due to psychoactive or analgesic effects”. Nevertheless, it recommended that “A high priority should be given to carefully controlled trials of cannabinoids in patients with chronic spastic disorders which have not responded to other drugs”. This view is shared by many of our witnesses.

5.24 The BMA report calls for the extension of the licensed indications for nabilone, and for the licensing of dronabinol, for use in MS and other chronic spastic disorders unresponsive to standard drugs. The wording of the report is ambiguous: on p 9 it says, “*Depending on the results of...trials* there may be a case for considering extension of the indications...”; on p 80 it says, “There is a case for the extension of the indications” for such use *pending* trials. The latter is repeated in the BMA’s written evidence to us (p 10). According to Professor Ashton the ambiguity is

inadvertent; and a letter from Professor Nathanson of the BMA (p 206) confirms that the BMA does indeed support licensing *pending* further research.

5.25 The National Drug Prevention Alliance suggest that this ambiguity reflects disagreement between Professor Ashton, the main author, and editors at the BMA. They would regard licensing in advance of trials as “an extraordinary aberration” (p 279). The Christian Institute say it would set “a very bad precedent” (p 208). In any case, the MCA are not prepared to allow anecdotal evidence as a substitute for clinical trials (QQ 168, 178, 189); and no application to extend the licence for nabilone has in fact been made (Q 191).

Pain

5.26 Besides MS, the other main indication claimed for cannabis-based medicines is the control of pain (analgesia). The BMA report says, “The prescription of nabilone, THC and other cannabinoids...should be permitted for patients with intractable pain”, especially in terminal illness.

5.27 Professor Wall told us that there is clear evidence of analgesic effects of cannabis and cannabinoids from animal experiments. Some of the results suggest that pain which originates from damaged nerves might respond to cannabinoids; this could be of medical value as this type of pain does not respond well to treatment with morphine and related narcotics (Q 99). An example of such pain is phantom limb pain following amputation (Q 100). As many as 30 per cent of amputees suffer from this distressing condition, for which there is currently no satisfactory treatment. Dr Colin Stewart, who works in the field of major limb amputation in Dundee, reports anecdotal evidence that cannabis can relieve this pain; he recommends that trials of cannabis be undertaken in such patients (p 304).

5.28 Dr David Lambert, of the University of Leicester, confirmed that there is evidence for analgesic actions of cannabinoids acting on both the spinal cord and higher brain centres. He and Dr Notcutt suggested that one way of dissociating the pain-relieving actions of cannabinoids from their psychoactive effects might be to deliver the cannabinoid locally to the spinal cord via the cerebrospinal fluid, as has been done with opiate analgesics (QQ 440–6).

5.29 Dr Anita Holdcroft of Hammersmith Hospital, a contributing author to the BMA report, has reported the results of a placebo-controlled trial of cannabis in a patient with severe chronic pain of gastrointestinal origin (diagnosed as familial Mediterranean fever)²¹. Treatment was with capsules of cannabis oil, standardised for THC content. The patient’s demand for morphine was substantially lower during treatment with cannabis than during a period of placebo treatment (p 224).

5.30 In short, there is scientific evidence that cannabinoids possess pain-relieving properties, and some clinical evidence to support their medical use in this indication. Many of our witnesses consider that high priority should be given to further research in this area.

Epilepsy

5.31 There is some anecdotal evidence to support the possible use of cannabis or cannabinoids in the treatment of epilepsy, but little more. Cannabinoids can exert both convulsant and anticonvulsant effects in various animal tests. Of greatest interest are the anticonvulsant properties of the naturally occurring cannabinoid cannabidiol; this compound is essentially devoid of the psychoactive effects of THC. The limited clinical data available on the use of cannabidiol in the treatment of epilepsy are, however, equivocal and based on very small numbers of patients. The BMA report concludes, “It could possibly provide a useful adjunctive therapy for patients poorly controlled on presently available drugs. THC and other psychoactive cannabinoids are probably not suitable as anticonvulsants”.

²¹ Holdcroft A *et al.* *Pain relief with oral cannabinoids in familial Mediterranean fever.* *Anaesthesia*, 1997, 52, 483.

Glaucoma

5.32 Cannabinoids cause a lowering of pressure in the eye both in animals and in man, although the site of action and the mechanism involved remain unknown. It has been suggested that cannabis or cannabinoids might be useful in the treatment of elevated intraocular pressure (IOP) in glaucoma, one of the commonest causes of blindness (see the BMA and WHO reports). Keith Green, Professor of Ophthalmology at the Medical College of Georgia, USA, told us the results of his own studies in more than 300 human subjects with both normal and raised IOP. Cannabis caused an average 25 per cent decrease in IOP which lasted for 3–4 hours. However, in order to maintain IOP at baseline levels, patients would have to smoke as many as 10 cannabis cigarettes a day, which is not practicable in view of the psychoactive effects of the drug and its ability to impair cognitive function. Professor Green calls for further research to determine the mechanisms involved, in order to see whether the desired ocular effects could be dissociated from the intoxicant effects (p 219; cp Appendix 3, paragraph 12). A similar view is expressed in the BMA and AMA reports, and by Professor Hall (Q 753).

Bronchial asthma

5.33 Cannabis and THC dilate the small airways of the lung, and this has suggested a possible application in the treatment of bronchial asthma. However, according to the BMA report, there have been few clinical trials and these were mostly in the 1970s before the advent of the more powerful drugs now available for the treatment of this illness. Smoked cannabis is clearly unsuitable for the treatment of asthma because of the irritant effects of the smoke, and THC delivered by aerosol also appears to have irritating effects. The Royal Society, however, conclude, "Cannabinoids...seem to be no less effective than conventional drug treatments. Further studies are required to improve cannabinoid formulation for administration as an aerosol" (p 294, cp Hall Q 753).

5.34 It is interesting to note that, if cannabis were effective in both glaucoma and bronchial asthma, it would be especially useful for patients suffering from both conditions, since many treatments for one of these conditions are contra-indicated for the other.

Need for clinical trials of cannabis and cannabinoids

5.35 As noted above, the Government consider that the burden rests on the proponents of wider medical use to satisfy the Medicines Control Agency that the proposed medicine fulfils the normal criteria of quality, safety and efficacy. Dr Brian Davis of the MCA (QQ 167–171) emphasised that efficacy can be established only by undertaking controlled scientific trials; anecdotal evidence is not acceptable. The BMA report and the Multiple Sclerosis Society (Q 389) accept this position.

5.36 The requirements for approval of a new medicine are summarised as follows by the Royal Pharmaceutical Society (p 290):

- “
- The active compound must be characterised chemically and physically;
 - The active compound must be presented in a standardised dosage formulation;
 - Adequate tests must have been conducted on its safety;
 - Adequate controlled clinical studies must have been conducted in well-defined disease entities and efficacy demonstrated objectively;
 - The evidence must have been published and subjected to peer review.”

No-one claims that cannabis, or any cannabis-based medicine other than nabilone and dronabinol, has yet passed any of these tests.

5.37 There have been few adequately controlled clinical trials to date on cannabis and the cannabinoids, except as anti-emetics (see above); those which have been published are listed in Appendix III to the BMA report. (For details of what constitutes a clinical trial, see Box 7.) In MS, there have been only six trials, with a total of only 41 patients. There is broad agreement that more and better clinical trials would be a good thing (eg DH Q 180, ACT p 28). As Dr Pertwee pointed out, there is an element of urgency: "Cannabis is already being used...We are not in a situation where we can wait and see" (Q 317). The situation is particularly urgent with respect to symptom control in MS, as the BMA report acknowledges, because of a current lack of treatments. Similarly, in analgesia (pain control), there has been no new drug for 20 years (Notcutt Q 411).

BOX 7: CONTROLLED CLINICAL TRIALS

The approval of new medicines for human use requires that they be tested rigorously in controlled clinical trials. "Controlled" means comparing the test drug with an inactive dummy or "placebo". Placebo tablets or capsules are prepared in such a manner that they cannot be distinguished from the active test drug. In a "double-blind" placebo-controlled trial neither the patient nor the doctor or nurse knows whether active drug or placebo is given to any particular patient; this information is held in coded form by a person not actively involved in the conduct of the trial and is not made available until the trial has ended. Patients are randomly allocated to placebo and test drug groups to avoid any possible bias in the selection of those who are to receive the active drug. The outcome of the trial should involve objective measurements wherever possible, using predetermined outcome measures or "endpoints". The success or failure of the trial is measured by criteria established in a written trial protocol before the start of the trial. The trial should include a sufficiently large number of subjects to provide statistically significant differences in outcome measures between the placebo and drug-treated groups.

A variant on the use of separate groups of patients to receive placebo or test drug is the so-called "crossover" design, in which the same patients receive placebo and test drug at different stages during the trial and are crossed over from one to the other after a "wash-out" period in a random order, so that the trial remains double-blind.

The conduct of any clinical trial involving patients must be approved by the Medicines Control Agency, who issue a Clinical Trial Certificate (CTX) if the detailed written protocol for the trial meets with their approval. In addition the conduct of a clinical trial requires the prior approval of the local Ethics Committee at the site where the study is to be conducted.

5.38 The BMA report called on the Clinical Cannabinoid Group (an informal network of interested researchers convened by Dr Pertwee), patient groups, pharmaceutical companies and the Department of Health to "work together to encourage" trials. In their written evidence the BMA say, "the accumulation of scientific evidence has been hampered by regulations restricting the use of cannabinoids to one clinical indication" [anti-emesis] (p 11). Following their report, the BMA met the Government's Chief Medical Officer in March 1998 "to discuss likely further actions in moving forward clinical trials of cannabinoids for therapeutic uses". At the meeting, it was agreed that an appropriate body to conduct such trials was required and that it should be an independent or institutional research organisation.

5.39 "Clinical trials are expensive, but the research funding bodies have no objection of principle to funding work in this field. The MRC report a shortage of high-quality research proposals in this area (Q 629); but they would be "supportive" of funding well-conceived clinical trials in this field, and would even be prepared to consider a grant application "out of turn" (QQ 638, 769). In February 1998 the MRC had three grants, one to Dr Pertwee and two to Dr Kendall; Dr Pertwee's has now finished, as has one of Dr Kendall's (Q 621). The Wellcome Trust had made nine grants since 1990: five project grants, including three to Dr Pertwee, and four

research career re-entry fellowship grants, all to colleagues of Dr Pertwee. The Multiple Sclerosis Society and the BMA are also willing to help fund a trial (MSSoc p 89; Q 769). The Department of Health do not normally fund trials, but might “facilitate” (Q 194). Besides the Wellcome Trust, Dr Pertwee’s research group in Aberdeen is also funded by the USA’s National Institute on Drug Abuse (part of the National Institutes of Health) and a pharmaceutical company (Q 252).

5.40 Professor Edwards (Q 19) questions the justification for carrying out expensive controlled trials with cannabis. He is concerned about the possibility of diversion to misuse of the drug. As a preliminary, he favours a series of smaller-scale clinical investigations in individual patients.

5.41 Several of our witnesses have commented on the difficulties of conducting clinical trials with cannabis. How can a standardised product be made available? What formulation is to be used? How can the dose be predicted for any particular medical condition? How consistent and predictable would blood levels of THC be (QQ 7, 8, 180, 781)? In addition, individual patients are likely to differ considerably in the dose needed to control their symptoms—as with the use of opiates in the control of severe pain, where Professor Wall points out that a tenfold range of doses is commonly observed (QQ 112–3).

5.42 Professor David Grahame-Smith, Chairman of the Advisory Council on the Misuse of Drugs (Q 8), raised the question of the difficulty of carrying out a double-blind placebo-controlled trial with a psychoactive agent, as the drug could easily be distinguished from the inert placebo. Professor Lader suggested that one solution to this might be to test cannabis by comparison with some other psychoactive drug, rather than against an inactive placebo. Other possibilities are to use doses of the active drug too small to have psychoactive effect; or to proceed with an inactive placebo, and find out at the end of the trial how far patients could tell whether they were receiving the active drug or the placebo (Q 779).

5.43 In addition to these practical problems, clinical researchers face extra legal hurdles, and a generally negative climate of opinion, because of the status of cannabis as a Schedule 1 controlled drug. We consider this problem, and what might be done about it, in Chapter 7.

5.44 Clinical trials are now under active consideration in several fora. First, Dr Geoffrey Guy, a pharmaceutical entrepreneur, has recently set up GW Pharmaceuticals, to conduct licensed research and develop cannabis-based medicines, in collaboration with HortaPharm BV of Holland (see Dr Guy’s evidence, and QQ 107, 135, 413–420, 447). The aim is to produce standardised whole-plant extracts, rather than single chemicals, from plants bred for standard cannabinoid content, with a non-smoking mode of administration offering the advantages of smoking without the harm, and to proceed via clinical trials to an application for a product licence. Dr Guy received licences to cultivate cannabis, and to possess and supply it for research, from the Home Office in June 1998. He is now recruiting patients for trials, with help from the ACT.

5.45 Dr Guy is confident that rigorous trials can be mounted, and that contamination of the plant material can be avoided. He advocates the use of plant-derived products, and cites the examples of gentamicin, papaveretum and digitalis as approved plant-derived products that contain complex mixtures of alkaloids. He believes that, by using controlled growing conditions and cloned cannabis plants, it will be possible to produce a herbal preparation of consistent composition with adequate quality controls. This position is reinforced by data from the Dutch organisation Maripharma (see Appendix 4 paragraph 14), who have been able to produce medical-grade herbal cannabis selected to have a consistent content of THC (10.7 ± 0.1 per cent) and a low content of other cannabinoids.

5.46 Secondly, following the meeting between the BMA and the CMO (see above, paragraph 5.38), the Royal Pharmaceutical Society have set up a “working party on therapeutic uses of cannabinoids”, chaired by Professor Sir William Asscher, a past Chairman of the Committee on Safety of Medicines. The group includes representatives of the NHS R&D Directorate, the MRC

and the Multiple Sclerosis Society, and researchers including Dr Pertwee. Its objectives are “to produce guidelines for pilot clinical trials for cannabinoids as proof of principle of their effectiveness, and to assist those who wish to conduct such trials to successfully complete them and publish the results”. The group has drawn up protocols for two trials: one for spasticity arising from MS, the other for post-operative pain. In each case the trial will be longitudinal (i.e. not a cross-over trial), involving three groups of patients: one will be given dronabinol, another an extract of cannabis containing the same quantity of THC, and the third a placebo. Smoking has been ruled out; administration will be by oral capsule. The lead clinician for the pain trial is Dr Anita Holdcroft, whose previous single-patient trial of cannabis was noted above; the lead clinician for the MS trial is Dr John Zajicek of Derriford Hospital, Plymouth. The protocols are to be launched shortly, at which point applications will be made for funding (from non-industrial sources) and for Home Office licences. (See the evidence of members of the working party, QQ 768–811.)

5.47 In addition, Jo Barnes of Exeter University is launching a pilot study of oral THC involving 30 MS patients, funded by the university, intended to “provide data which can be used for a sample size calculation for a full-scale study” (p 217). Dr Robson is planning pilot studies using nabilone and dronabinol for detoxification from opiates and as an anxiolytic/hypnotic in acute drug-related problems (p 118, Q 458). Professor Wall knows of three other United Kingdom trials at an advanced planning stage, by Dr Pertwee, Dr Notcutt (Q 448), and Dr Clare Fowler at the National Hospital for Neurology and Neurosurgery in London.

5.48 These various initiatives are, or may become, interrelated. The Asscher group trials, and others, may use GW Pharmaceuticals as the source of supply of cannabis material; in that case they might be covered by an extension of Dr Guy’s Home Office licence. The Exeter group, and others, may bring their trials within the Asscher group’s protocols, so as to become part of a national study. In the end, it is possible that all or most of these initiatives will come together into two national trials, using the Asscher group’s protocols and Dr Guy’s licence and materials.

Should clinical trials be limited to cannabinoids?

5.49 Both Dr Guy and the Asscher group propose to conduct trials involving extracts of herbal cannabis; but according to several of our witnesses this may be a mistake. Professor Ashton and Professor Nathanson of the BMA (Q 55), reflecting the position of the BMA report itself, argued strongly in favour of trials of synthetic cannabinoids rather than herbal cannabis, because of the difficulties of obtaining standardised preparations of the plant material. Both Dr Guy and the Asscher group believe that they can solve the problem of standardised preparations.

5.50 The Association of Chief Police Officers argue that clinical research should be confined to individual cannabinoids: ACPO believe that cannabis is a harmful substance, the control of which must be continued (p 196). The Christian Institute take a similar view, arguing *inter alia* that medical use might serve as a front for legalisation (p 208). (We consider this argument below in Chapter 7.) Mary Brett, Head of Health Education at Dr Challoner’s Grammar School²², writes, “All scientific evidence is unequivocal in favour of maintaining prohibition of crude marijuana for both medical and recreational use. However, purified cannabinoids may, after rigorous testing and clinical trials in comparison with other and existing treatments, prove to be beneficial in certain disorders ...” (p 206).

5.51 Others, however, favour research on herbal preparations derived from cannabis. Professor Wall argues in favour of trials of cannabis rather than pure cannabinoids. He criticises the BMA report for recommending that trials be confined to synthetic cannabinoids (p 32); he considers that it would be premature at this stage of our knowledge to assume that the only active substance in cannabis is THC (Q 103). We have received anecdotal evidence that users who have tried cannabis and nabilone and/or dronabinol prefer cannabis (LMMMSG p 271; ACT pp 28, 30; IDMU p 228).

²² Mrs Brett has written widely on cannabis, and advises the NDPA.

5.52 The Royal Society (p 295) also conclude that “Several components of cannabis might be required to reproduce the effects seen with the whole drug”. Others in favour of including cannabis itself in any programme of trials include the Royal Pharmaceutical Society (p 284), Dr Kendall (p 268), Dr Pertwee (QQ 266, 315), Dr Robson (Q 480), Dr Stewart and Dr Schon. The Multiple Sclerosis Society (Q 352) point out that cannabis is available, and is what existing medical users are using; the ACT observe that including it in trials would permit existing users to regularise their position (by enrolling for trials) without changing their medication (Q 149). Professor George Radda, Chief Executive of the MRC, would not rule out extracts of herbal cannabis; “but we must know the composition” (Q 645).

5.53 Some witnesses point out that the variable chemical composition of herbal cannabis can be turned to medical advantage. The London Medical Marijuana Support Group argue that differing strains of cannabis containing different proportions of THC, cannabinol (CBN) and cannabidiol (CBD) might have different medical effects: “The more CBN and CBD, the greater the intensity of body related sensations; the less CBN and CBD and the more THC, the more mentally active the stimulation will generally be. High CBN and CBD cannabis is more effective for the control of symptoms which are generally felt as being body related, such as chronic pain” (p 270). Neil Montgomery also maintains that cannabis resins of different geographic origin elicit distinct patterns of psychoactive effect (Q 594). There is, however, no scientific evidence available on these topics.

Should clinical trials include smoking?

5.54 Both Dr Guy and the Asscher group have ruled out smoking for the purposes of their trials; and many of our witnesses would support them (e.g. Notcutt p 104, Henry p 224, RPharmSoc p 284, Wall Q 103, Pertwee QQ 266, 315, MSSoc Q 364, ACT Q 154). Smoking is felt to carry too great a potential health risk: see Chapter 4. However, as noted above, there are anecdotal reports that those who use cannabis for medical purposes favour smoked cannabis over orally administered cannabinoids such as nabilone. The perceived advantages of smoked cannabis may be due to the rapid absorption and flexibility of dose-control offered by smoking as a route of administration: see Chapter 3.

5.55 Dr Robson suggested that there should be a comparison in clinical trials between smoked cannabis and smoked THC (Q 480). The Asscher group’s proposal, to compare orally administered THC with an orally administered cannabis product, will achieve the same result, namely a comparison of like with like.

5.56 There is considerable discussion of possible improvements in the mode of administration of cannabis and synthetic cannabinoids (e.g. QQ 60, 266–273). IDMU (p 235) described recent research in the United States on the ability of various methods of smoking herbal cannabis to reduce tar intake relative to THC. Surprisingly, the use of a water pipe, in which the cannabis smoke is passed through water prior to being inhaled, and the use of a vaporiser, in which herbal cannabis is heated but not burned, had relatively little effect in reducing the amount of tar inhaled. Unfortunately the slow and unreliable absorption of herbal cannabis and synthetic cannabinoids taken by mouth can lead to both under- and over-dosing. Other possibilities include the development of inhalers (e.g. Guy QQ 713–4), sprays, rectal suppositories (see Appendix 3, paragraph 3) and skin patches, and a sub-lingual method (taking a tincture under the tongue—LMMSG p 270). Research on such alternative delivery systems is held to be a high priority by many witnesses.

5.57 Although there is general agreement that smoked cannabis carries a potential risk for long-term users, the medical application of smoked cannabis is not ruled out by all. The US National Institutes of Health report says, “...there might be some patient populations, e.g. cancer patients experiencing nausea and vomiting during chemotherapy, for whom the inhalation route might offer advantages over the currently available capsule formulation [of THC]”. They conclude, “In summary, the testing of smoked marijuana to evaluate its therapeutic effects is a difficult, but not impossible, task”. The American Medical Association report recommends “that adequate and

well controlled studies of smoked marijuana be conducted in patients who have serious conditions for which preclinical, anecdotal or controlled evidence suggests possible efficacy including AIDS wasting syndrome, severe acute or delayed emesis induced by chemotherapy, multiple sclerosis, spinal cord injury, dystonia [involuntary muscle movements, e.g. a tic], and neuropathic pain...". Among our witnesses, those who would include smoking in trials include Dr Schon (p 304), Dr Stewart (p 305) and Dr Robson (Q 480); and Professor Radda of the MRC would be prepared to do so, provided that the trial protocols were satisfactory (QQ 646, 654).

CHAPTER 6 RECREATIONAL USE OF CANNABIS

Prevalence

6.1 Cannabis is by far the most widely used illicit drug in the United Kingdom, as in most other Western countries; and almost all of this use is for recreational rather than medical purposes. According to the Department of Health, "Cannabis is now the third most commonly consumed drug after alcohol and tobacco" (p 47).

6.2 Cannabis dominates the drug crime statistics, and the figures are rising. Figures for the whole United Kingdom for 1996 (*Home Office Statistical Bulletin* 10/98) show that 72,745 drug offenders (77 per cent of the total) committed offences involving cannabis (alone or with other drugs). There were 91,432 seizures of cannabis in 1996 (75 per cent of the total for all drugs) and this involved record quantities of cannabis resin (66,921 kg), herbal cannabis (34,373.6 kg) and cannabis plants (116,119 plants). These figures, which are the most recent available, represent more than a three-fold increase over 1990, with a particularly sharp increase in the number of offences related to the cultivation of cannabis plants and the numbers of plants seized.

6.3 It is difficult to put a figure on the prevalence of cannabis use in the United Kingdom. The Parliamentary Office of Science and Technology, in their *Cannabis Update* of March 1998, gave figures from the British Crime Survey 1994 which indicate that in the adult population (16–59) 1 in 5 had "ever tried" cannabis (1 in 20 within the previous month) and in the 16–29 age group just over 1 in 3 had "ever tried" cannabis (1 in 20 within the previous month). These figures are not dissimilar to those in the WHO report for other countries in Europe²³, with somewhat higher figures for the USA, Canada and Australia. They suggest that as many as 7.5m people aged 16–59 in the United Kingdom have used cannabis at least once, and that between 1.5m and 2m take the drug at least once a month (cp Montgomery Q 559). The Royal College of Physicians have established a Joint Working Party with the Royal College of Psychiatrists which among other matters will review the epidemiology of illicit drug use in the United Kingdom.

Pattern of use

6.4 The pattern of cannabis consumption in the United Kingdom varies according to geography, socio-economic conditions and the age of the user. Professor Edwards observed that cannabis is and has been used in very different ways in different times and places; for instance, there are people in south London who smoke 20 joints a day (Q 26). Dr Robson cautions that much of the use of cannabis in the community does not come to the attention of the health services or the police, and therefore little is known about it (Q 456).

6.5 The Independent Drug Monitoring Unit conducted a survey of 1,333 regular cannabis users who attended a major pop festival in Britain in the summer of 1994 (p 231). The majority were daily cannabis users with an average consumption of about 24.8g of cannabis resin per month. Respondents gave highly positive subjective ratings to cannabis (as opposed to negative subjective ratings to solvents, cocaine and heroin). More than 60 per cent believed that cannabis had been of benefit to their physical or mental health. They would prefer that the law was more liberal, but a majority (70 per cent) did not think that they would use more if it was.

6.6 Dr James Robertson, a GP working in Edinburgh, has reported the results of a survey (funded by the Royal College of General Practitioners) of 328 consecutive patients attending his surgery (average age 33.7 years)²⁴. 200 patients (61 per cent) said that they had used cannabis at least once, and more detailed interviews of 101 of these revealed that 90 were regular users, with 67 using cannabis on a daily basis. Most spent £25 or less per week on cannabis, but a small number of individuals spent £100 or more per week.

²³ See also the *Annual Report on the State of the Drugs Problem in the EU 1997*, by the European Monitoring Centre for Drugs and Drug Addiction.

²⁴ Br. J. Gen. Pract. 1996, 46, 671.

6.7 Neil Montgomery described for us various ways to take cannabis recreationally (QQ 544–554). He divides recreational users into three groups:

- Casual Irregular use, in amounts up to 1g of resin at a time, to an annual total of no more than 28g (Q 545);
- Regular Regular use, typically of 0.5g of resin a day (equivalent to 3 or 4 smokes of a joint or pipe), adding up to about 3.5g per week (Q 548);
- Heavy More or less permanently stoned, using more than 3.5g of resin per day and 28g or more per week (Q 554). The smallest group, around 5 per cent. “The extent to which a heavy user can consume cannabis is largely unappreciated.”

Herbal cannabis appears to be consumed at twice the rate of cannabis resin, presumably because of its lower content of THC. Comparable data are provided by IDMU (pp 231–3).

6.8 According to POST’s *Cannabis Update*, 9 per cent of ever-users use cannabis daily, and 14 per cent several times a week, making it of all illegal drugs the one most likely to be used regularly. According to Professor John Strang, Director of the National Addiction Centre, few users end up in hospital with acute psychiatric problems, and most regular users are not nowadays advised by their doctor to change their habits (Q 244). For the risk of dependence, see Chapter 4.

6.9 Many cannabis users also consume a variety of other psychoactive agents. As the commonest method of using cannabis in the United Kingdom is to smoke cannabis resin mixed with tobacco, nicotine use is very high among cannabis users. Among other things, this makes it difficult to assess the respiratory risks of smoked cannabis as they are confused with the well-established risks of smoked tobacco. Alcohol use is also common, but regular cannabis users may consume less than non-cannabis users. Drug treatment clinics often see poly-drug users, who are consuming a variety of illicit substances, of which cannabis is commonly one (QQ 42, 216, 487, 515, 562; DH p 47).

6.10 According to the Department of Health, most cannabis users have discontinued by their mid to late 20s (p 46); and of those who have ever been daily users, only 15 per cent persist with daily use in their late 20s (p 45). Neil Montgomery has identified a group of regular users who stop in their 30s and start again in their 50s (Q 575).

Content of cannabis consumed in the United Kingdom

6.11 Some of our witnesses expressed concern that the preparations of illicit cannabis used in the United Kingdom today are more potent than previously, exposing users to a greater risk of acute intoxication and long-term adverse effects. Professor Ashton (p 12) suggested that “a typical 1970s ‘reefer’ contained about 10mg of THC..., while a typical ‘joint’ today may contain 60–150mg or more of THC. This increase in potency results from sophisticated plant breeding and cultivation methods leading to highly potent varieties of cannabis, such as Skunkweed”. Other witnesses made similar assertions (e.g. Q 33).

6.12 However, the Home Office Forensic Science Service, who have data on the THC content of seized cannabis samples, do not support the view that most users in the United Kingdom are exposed to material containing ten times as much THC as in the 1960s and 1970s. They say, “Cannabis resin...has a mean THC content of 4–5 per cent, although the range is from less than 1 per cent to around 10 per cent. This pattern has remained unchanged for many years” (p 218). Cannabis resin, imported most commonly from Morocco, Afghanistan or Pakistan (IDMU p 230), is the form of cannabis most widely used in the United Kingdom, and accounted for two thirds by weight of all seized material in 1996 (*Home Office Statistical Bulletin* 10/98). One of our witnesses, a user and convicted dealer, claimed that most modern cannabis is in fact weaker than material from the 1960s.

6.13 On the other hand, there appears to have been an increase in the THC content of herbal cannabis—probably because of the use of new strains of cannabis plant and improved growing conditions. In the United States, the University of Mississippi have analysed the THC content of seized cannabis on behalf of the US government since 1980 (see Appendix 4, paragraph 13). They report an increase in the THC content of herbal cannabis from around 2 per cent in 1980–81 to more than 4 per cent in 1997. The Forensic Science Service report that herbal cannabis in the United Kingdom currently also contains an average of 4–5 per cent THC. They also report that cannabis grown in the home, using improved growing techniques and improved plant varieties, now produces herbal cannabis with a considerably higher THC content, with an average close to 10 per cent THC and a range extending to over 20 per cent (p 218). Use of “hydroponic” cannabis (grown in a nutrient solution rather than in soil) appears to be increasing rapidly, with plant seizures in the United Kingdom up from 11,839 plants in 1992 to 116,119 in 1996.

6.14 Professor Hall suggested, “More potent forms of cannabis need not inevitably have more adverse effects on users’ health than less potent forms. Indeed, it is conceivable that increased potency may have little or no adverse effect if users are able to titrate their dose to achieve the desired state of intoxication. If users do titrate their dose, the use of more potent cannabis products would reduce the amounts of cannabis material that was smoked, thereby marginally reducing the respiratory risks of cannabis smoking” (p 221; cp IDMU p 235).

6.15 The overall quality of imported cannabis resin appears to have fallen in recent years; many users perceive cannabis resin as adulterated and forensic analysis frequently confirms that this is the case, with the addition of caryophyllene, a constituent of cloves, being particularly common (IDMU p 230; Montgomery p 132 and QQ 577, 589). Yet Professor Hall considers that concern about herbicide contamination is unfounded, and that case history evidence of health problems from microbial contamination is limited. Neil Montgomery calls for research in this area.

The state of the law

6.16 This Government show no sign of taking a softer line against recreational use of cannabis than their predecessors. According to the White Paper *Tackling Drugs* (Cm 3945) of April 1998, “The more evidence that becomes available about the risks of, for example, cannabis...the more discredited the notion that any of the substances currently controlled under the 1971 Act are harmless”. This echoes the view of Professor Edwards of the ACMD: “We are in a rapidly changing field of knowledge”; and new knowledge is making cannabis look more dangerous, not less (QQ 21, 27).

6.17 Most of our professional witnesses agree that the adverse effects of cannabis fully justify prohibition (e.g. Henry/RCPATH p 224). The only argument on the other side is that cannabis is arguably less dangerous than alcohol or tobacco (e.g. RCGP p 281, Kendall p 268). Professor Hall acknowledged this, but noted “the difficulty in predicting the effect that relaxation of cannabis prohibition would have on current patterns of cannabis use and the harms caused by that use” (p 222).

6.18 The Under-Secretary of State at the Home Office, George Howarth MP, told us confidently that legalising recreational use would cause such use to increase (Q 674). Professor Edwards, writing for the Royal Society, is less sure: “We would expect weakening of controls over cannabis to result in increased use levels, but this is an empirical question on which research at present is not conclusive...Removal of prohibition on cannabis would have to be described as a voyage into the unknown. Some added harm and some added costs would undoubtedly result” (p 303). There is international experience which might throw light on this question, but we have not explored it in detail.

6.19 We have not considered the wider range of social and criminological issues which would be raised by any proposal to change the law on recreational cannabis use. These include enforcement, the impact on use of other illegal drugs, and the international context and the danger of “drug tourism”; as well as ethical, philosophical and religious questions about the freedom of

the individual, the nature of society and the morality of mind-altering drugs. As we said when we began this enquiry, these matters fall outside our remit as a Science and Technology Committee. An Independent Inquiry into the Misuse of Drugs Act, chaired by Lady Runciman of Doxford and supported by the Police Foundation, is currently considering the matter in its wider context; they expect to report next year.

CHAPTER 7 CHANGING THE LAW ON MEDICAL USE AND RESEARCH: REVIEW OF THE EVIDENCE

7.1 In law, it would be possible to make cannabis and/or additional cannabinoids prescribable by moving them from Schedule 1 to Schedule 2 to the Misuse of Drugs Regulations, in advance of any cannabis-based medicine being licensed and reaching the market. However, the Government are not willing to reschedule cannabis in advance of licensing. Licensing depends on research and clinical trials: the Government are satisfied with the arrangements for allowing research and trials, but some of our witnesses are not. In the mean time, medical use remains illegal.

Prosecution for use of cannabis for medical purposes

7.2 It is not known what proportion of prosecutions for possession of cannabis arise from medical use. The ACT drew our attention to 15 reported cases of people charged with cultivation, possession and/or supply in medical situations since 1996: of the 12 cases where the outcome was known, one resulted in a sentence of 50 hours' community service; in the other 11, either the prosecution was abandoned, the defendant was acquitted, or the sentence was no greater than a conditional discharge. IDMU offer further figures (p 258); they comment that, although outcomes in such cases are highly variable, juries seem more likely to acquit "where there is convincing medical evidence, given similar circumstances concerning paraphernalia".

7.3 People who use cannabis for medical purposes face prosecution if caught cultivating or possessing cannabis; but, according to Austin Mitchell MP, "It is bringing the law into a certain amount of difficulty and disrepute because either the police are cautioning or the courts are giving very lenient sentences" (Q 132). Dr Pertwee considers it unsatisfactory that such people are sometimes prosecuted, unsatisfactory that law-breaking is sometimes tolerated, and unsatisfactory that the position is inconsistent around the country (Q 313).

7.4 The BMA report recommends, "While research is under way, police, the courts and other prosecuting authorities should be aware of the medicinal reasons for the unlawful use of cannabis by those suffering from certain medical conditions for whom other drugs have proved ineffective" (cp Q 55). Similarly the Multiple Sclerosis Society want the law to treat people caught using cannabis for medical reasons in an "appropriately compassionate fashion" (p 90). They report that most people convicted in such circumstances receive a suspended sentence; but they are concerned about the way the system treats people as much as about the verdict (Q 341; cp IDMU p 261).

7.5 Mr Howarth, the Under-Secretary of State, declined to comment on how the Crown Prosecution Service and the courts treat such cases (QQ 668–673), beyond observing that in some cases the plea-in-mitigation of medical use might be trumped-up (Q 674). The Home Office added that official statistics do not distinguish between cases with a medical aspect and cases without; but that, on the anecdotal evidence, outcomes in medical cases were not obviously out of line with outcomes in purely recreational cases (Q 675). (The proportion of persons in the United Kingdom dealt with for possession of cannabis who are cautioned rather than prosecuted rose from 35 per cent in 1986 to 62 per cent in 1995—*Home Office Statistical Bulletin* 10/98.)

Possible transfer from Schedule 1 to Schedule 2

7.6 According to the Home Office (p 150), cannabis could be transferred from Schedule 1 to Schedule 2 by statutory instrument, subject to negative resolution in Parliament. The ACMD would have to be consulted first. According to the Minister (Q 676), under the 1961 UN Convention, rescheduling cannabis itself and cannabis resin would not require international agreement; but, under the 1971 Convention, rescheduling cannabinol and its derivatives other than dronabinol would require prior amendment of the Schedules to the Convention through the WHO and the UN Commission on Narcotic Drugs, as happened in the case of dronabinol in 1995.

7.7 Rescheduling would allow doctors to prescribe; but the Home Office say, "Our understanding is that the ability of doctors to prescribe cannabis would be hampered in practice if a cannabis-based medicine had not been granted a marketing authorisation by the MCA". The

Minister said that there were “compelling policy reasons” for requiring an MCA licence first (Q 676). When asked to explain the practical difficulties, he referred to the extra burden of responsibility which a doctor takes on by prescribing an unlicensed medicine (Q 679); he queried the wisdom of permitting prescription without proof of safety and quality (Q 680); and he noted that the ACMD had not called for change (Q 688).

7.8 Rescheduling would also allow doctors and pharmacists to manufacture and supply (Q 680); anyone else, including a pharmaceutical company, would require a Home Office licence. It would not in itself disapply section 8 of the Misuse of Drugs Act, which makes it an offence to allow cannabis to be smoked on premises; but this could be done by secondary legislation (Q 684).

7.9 So the Government *could* reschedule cannabis; the next question is, whether they should. Dr Lambert says, “Many patients are already illegally using cannabis...Their needs must be addressed whilst formal studies are undertaken”²⁵. IDMU finds the present position “inhumane”, and “unjustifiable both on moral and on public health grounds” (p 229). Dr Pertwee says (p 68), “A strong case can be made on the grounds of common sense and compassion for allowing doctors to prescribe...(oral) cannabis now for serious symptoms including muscle spasms”; but he admits that it will take better evidence to persuade the Department of Health (Q 263; see also paragraph 7.15 below).

7.10 Dr Robson described the present position as an “affront to humanity” (Q 460). He called for “compassionate reeferers” for AIDS and cancer patients (p 118), and possibly for patients with non-terminal conditions who might feel that the increased risk of cancer was worth taking (Q 469). He suggested that patients might be made to confirm in writing that the doctor had explained the risks; and that, if it were felt necessary, the number of doctors entitled to prescribe cannabis could be limited, as in the case of diamorphine (heroin) or cocaine prescribed for addicts under the Misuse of Drugs (Supply to Addicts) Regulations 1997 (Q 471). He added that research into synthetic cannabinoids might soon make herbal cannabis obsolete; but, in the mean time, “it just is not a dangerous enough drug for me to want to ban it” (Q 472).

7.11 The ACT want “medical preparations of natural cannabis...to be made available on a doctor’s prescription while research is going ahead” (p 28), by moving cannabis from Schedule 1 to Schedule 2 (Q 133). They argue that “we know now that cannabis can be effective and is safe enough to be prescribed by a doctor...and there are people who need treatment now”. Similarly, six of our witnesses, all users of cannabis for medical purposes themselves, want cannabis to be prescribable or otherwise legalised for medical use. 195 out of 200 respondents to the *Disability Now* survey, of whom 192 were disabled and 134 had taken cannabis for medical purposes, wanted such use to be legalised.

7.12 The London Medical Marijuana Support Group (p 271) consider the issue to be one of patients’ rights: “Please do not continue to make sick people criminals”. They call for either rescheduling, or a new system involving registration of patients. They would solve the problem of supply by allowing patients to grow their own, or by setting up co-operatives, or by permitting commercial cultivation. They argue that different users get benefit from different preparations; so they do not want a standardised preparation—though this would be better than nothing.

7.13 If the law cannot be changed, it could in theory be applied with flexibility. IDMU suggest “directives to the CPS on criteria to use when deciding whether a prosecution of a medical cannabis user is in the public interest” (p 225). According to the Home Office, however, systematic non-enforcement would be “quite unacceptable” (Q 671).

7.14 Though some witnesses to this Committee favour immediate transfer from Schedule 1 to Schedule 2, others are against it. Professor Radda insisted that anecdotal evidence, however large in volume, was not sufficient reason for rescheduling (Q 657). Sir William Asscher considers

²⁵ Hirst R A, Lambert D G and Notcutt W G, *op. cit.*

that immediate rescheduling would actually threaten proper trials, such as those proposed by his working party (see Chapter 5), by encouraging patients to use cannabis in an uncontrolled way rather than enrolling for the trial and risking receiving a placebo (Q 808).

7.15 The Multiple Sclerosis Society want sufferers to be able to make “informed choice about therapeutic agents”; therefore they would not support prescription of cannabis for MS in advance of proper trials (p 90, Q 368). The Royal Society say that, pending proper trials, “There is no persuasive case for the non-experimental medical use of cannabis”; and they are against smoking (p 295). The Royal Pharmaceutical Society take the same line (p 289); so does Professor Strang, who would be worried if cannabis were given “some easy track” (Q 249); so does Edward Jurith, on sabbatical in Manchester from the post of General Counsel to the White House Office of National Drug Control Policy (p 265). The Christian Institute agree: “The rules must remain the same for all substances...Rescheduling cannabis would declare that cannabis is suitable for medical use. The studies have not been done to demonstrate this” (p 207). They add that permitting cannabis to be smoked “would profoundly damage current health promotion attempts to dissuade smoking”. They suggest that other steps might be taken to help MS sufferers who are resorting to cannabis. Dr Pertwee considers that permitting prescription of cannabis could not be justified until both nabilone and dronabinol had been tried and failed (Q 314).

7.16 The BMA report recommends, “The WHO should advise the UN Commission on Narcotic Drugs to reschedule certain cannabinoids under the UN Convention on Psychotropic Substances, as in the case of dronabinol [which was rescheduled in 1995]. In response the Home Office should alter the Misuse of Drugs Act accordingly.” Alternatively, “The Government should consider changing the Misuse of Drugs Act to allow the prescription of cannabinoids to patients with particular medical conditions that are not adequately controlled by existing treatments”. On the other hand, David Nutt, Professor of Psychopharmacology at the University of Bristol²⁶, considers that the availability of nabilone, which may be prescribed on an unlicensed basis for any of the conditions identified by the BMA, makes it unnecessary to change the law (p 280).

7.17 The Royal Pharmaceutical Society caution that, if unlicensed use of cannabinoids becomes more common (as the BMA think it might, following their report—Q 83), there should be “full consultation between the medical and pharmacy professions” (p 290). They urge the Government to consider moving all cannabinoids from Schedule 1 to Schedule 2.

Research

7.18 As noted in Chapter 3, cannabinoid pharmacology is currently a lively field of research. However, until Dr Guy’s initiative, no new cannabis-based medicines were in commercial clinical development (Wall Q 134). As to why this should be so, most of our witnesses point to the “stigma” of working with a “disreputable” substance and a Schedule 1 controlled drug (e.g. Austin Mitchell MP Q 132, Pertwee Q 317, Robson Q 482). Others point to the likelihood that a non-synthetic cannabis-based medicine would be cheap and therefore unprofitable, and the markets for it small (RPharmSoc p 289; Lader QQ 7, 17)—though Professor Ashton and the BMA believe that the global market is potentially large (Q 57). Dr Pertwee believes that drug companies are very interested in the possibility of cannabinoids which avoid psychotropic effects by acting only on the CB2 receptor (Q 281); they are “dying to get in there, but they do not know what to do” (Q 295).

7.19 Dr Notcutt believes that what puts companies off research involving a Schedule 1 drug is not the stigma, but the “sheer difficulty” (Q 414). The principal additional difficulty is the requirement to obtain a licence from the Home Office (see Box 8). If cannabis were moved to Schedule 2 to the Regulations, research licences would no longer be required (Q 677).

7.20 In addition to the lack of commercial development work, there is little clinical research in this area. Professor Wall comments, “It is a paradox that a subject of such intense scientific

²⁶ A member of the Independent Inquiry into the Misuse of Drugs Act—see paragraph 6.19.

BOX 8: CANNABIS RESEARCH LICENCES

Licences to possess any Schedule 1 drug for research may be granted by the Home Office under section 7 of the Misuse of Drugs Act and Regulation 5 of the Misuse of Drugs Regulations. The Under-Secretary of State at the Home Office, George Howarth MP, explained to us the conditions under which licences are granted (Q 662). There must be a legitimate reason for the research; details of method and timetable; ethical approval; and safeguards including safe custody and record-keeping. The research would normally be expected to be conducted at a university hospital or pharmaceutical company; and the method of administration must allow for control of dosage. According to the Home Office, there have been a total of 27 applications for cannabis research licences, of which 25 have been approved and two agreed in principle; no application for a licence has been refused (HC WA 255, 18 Dec. 1997).

The Home Office supplied us with a list of 22 current licences. All are granted to named researchers, 20 at universities and two in hospitals. Most are for teaching or testing purposes; only three appear to be for research. Four of the licences were issued this year, compared with 22 over the previous 24 years; the Home Office attribute the increase to a Royal Pharmaceutical Society symposium on medical uses of cannabis in July 1997 (Q 666). There are 80 current research licences for Schedule 1 substances other than cannabis (Q 665). Among our witnesses, cannabis research licences are or have been held by Dr Pertwee, Dr Schon (see p 303 and Q 664), Dr Holdcroft (see paragraph 5.29), and Dr Guy (see paragraph 5.44); and Jo Barnes has a licence "in principle" for the Exeter pilot study (see paragraph 5.47).

interest should receive so little clinical attention. One reason...[is] the daunting and excessive bureaucratic control which artificially separates studies of cannabis from drugs such as narcotics. The other reason is the general social atmosphere which labels cannabis with every possible negative attitude" (p 31, cp Q 143). He compares the attitude to medical use of narcotics before the work of Dame Cicely Saunders (Q 127). Similarly Dr Lambert says, "The Schedule 1 status of cannabis has made modern clinical research almost impossible, primarily because of the legal, ethical and bureaucratic difficulties in conducting trials with patients. In addition, the general attitude towards cannabis...has not helped"²⁷. This is regrettable, since there is "a wide range of possibilities and a massive opportunity for research". The Royal Pharmaceutical Society blame the "disappointing" lack of evidence on the "stigma" attached to cannabis, and the burden of licensing (p 288).

7.21 Professor Hall also believes that research has been chilled by the link with recreational use. He regards this link as "spurious". He observes, "The recent discovery of the cannabinoid receptor may help to overcome some of the resistance...by holding out the prospect that the psychoactive effects...can be disengaged from [the] other therapeutically desirable effects" (p 222). The Multiple Sclerosis Society believe that the stigma attached to cannabis as a medicine can be countered by "raising awareness" and taking the issue seriously, which to some extent has already happened (Q 372); and they know of numerous volunteers for trials (Q 389).

7.22 Dr Holdcroft notes two further difficulties: the lack of standardised preparations (she produced her own capsules), and the medicolegal problems of working with cannabis-naïve subjects²⁸. Dr Notcutt blames the licensing system, and the problem of supply (Q 413); he is optimistic that Dr Guy's initiative may surmount both obstacles. Austin Mitchell MP believes that ethical committees "run a mile" from sanctioning clinical research using a Schedule 1 drug (Q 132). Professor Edwards likewise points to ethical problems (Q 19); he recommends, before blind trials,

²⁷ Hirst R A, Lambert D G and Notcutt W G, *op. cit.*

²⁸ Holdcroft A *et al*, *op. cit.*

“a small series of open clinical investigations with repeat and careful observations on the individual patient”. The National Drug Prevention Alliance, noting that the prospective markets may be too small to warrant the commercial cost of trials, suggest that trials might be grant-aided from public funds (p 279—they regard this as preferable to licensing without trials).

7.23 The Department of Health say, “Both the Home Office and MCA have always indicated that they are prepared to look sympathetically at well-founded research proposals in this area” (p 48, cp Q 167). However Dr Kendall calls for “relaxation of the level of control” over trials (p 268). Dr Robson, in his review for the Department, says, “Research will only be possible if the regulations imposed under the Misuse of Drugs Act are made more flexible”. IDMU say (p 229), “The present licensing system and policy has severely limited research opportunities and should be reviewed”; given the rise in research activity noted above, the United Kingdom academic community and pharmaceutical industry may miss opportunities if the research licensing regime is not relaxed.

7.24 Yet the Multiple Sclerosis Society believe that the present system obstructs research more by its effect on attitudes than by practicalities (Q 388); and it is the impression of Austin Mitchell MP (Q 132) and Clare Hodges (Q 136) that the Home Office are already more flexible than they used to be. Professor Radda believes that a good research proposal will receive a licence without difficulty, and that scientists today are well used to regulation of this kind (Q 630). Dr Guy says that, although consultation was lengthy (from application to grant took 4 months—Q 663), the Home Office have been “most helpful” (p 162).

7.25 The BMA report said, “The regulation of cannabis and cannabinoids should be sufficiently flexible to allow such compounds to be researched without a Misuse of Drugs Act licence issued by the Home Office”. In evidence, the BMA reported “very positive feedback” from the Department of Health and the Home Office on the pace of the licensing process (Q 82); but they said that at present there was serious delay (Q 92). The Home Office responded, saying, “Applications for research licences are dealt with as expeditiously as the circumstances allow” (p 149); the Minister gave the time from application to grant in the last six cases, which averaged seven weeks (Q 663). The BMA hope that guidelines for trials would help to accelerate the process (Q 92).

7.26 The Committee put to the BMA the idea of a meeting between the Home Office and researchers, and they welcomed it (Q 93). The Home Office say that they would be happy to hold such a meeting, jointly with the Department of Health: “It would provide a useful opportunity to highlight some of the complex issues involved such as the supply of standardised cannabis, and the adoption of sound methodologies”. Work is now in hand to set up such a meeting (Q 686).

Medical use and recreational use

7.27 “Without pressing the panic button”, Professor Edwards points out that cannabis or preparations of cannabis supplied for medical use might be diverted to recreational use (Q 20). Professor Hall warns that, if doctors were allowed to prescribe cannabis, some might be tempted to profit from bogus prescriptions (Q 761). New Department of Health guidelines on clinical management of drug abuse are to cover “leakage” of prescribable controlled drugs (such as methadone) onto the black market; the Department comment that leakage of nabilone is “highly unlikely”, since it is dispensed only by hospital pharmacies in small amounts (p 217). The BMA report says, “It would be prudent to develop a labelling system that does not identify prescribed drugs as cannabinoids, and to warn patients that such drugs should be kept in a place inaccessible to others”. Professor Nathanson added that, ideally, cannabis-based medicines would be developed which had minimal psychoactive effects (Q 76).

7.28 On 23 January 1997, the then Under-Secretary of State, Home Office, told the House of Commons, “Many of those calling for the medical use of cannabis are using it as a stalking horse to promote the campaign for its legalisation” (HC col. 1060). David Copestake, a Methodist Minister who has researched and written in this field, takes this view; he observes that medical uses

were once touted for tobacco (p 213). The NDPA say the same, claiming that the BMA has been “hi-jacked” and that the ACT are “very familiar” with lobbyists for legalisation (p 278). The Christian Institute agree (p 208).

7.29 The ACT insist that they are not calling for general legalisation (p 28). They point out that heroin (diamorphine) may be prescribed (it is a Class A drug under the Misuse of Drugs Act, yet in Schedule 2 to the 1985 Regulations). Dr Notcutt observes that there is no evidence that heroin abuse is thereby encouraged, and lists several other drugs of potential abuse which are used unlicensed in chronic pain (p 105). The MRC make the same point, and say (as do several other witnesses), “The question of potential medical uses for cannabis and its derivatives must be considered quite separately from the question of prohibition of recreational use” (p 144). According to Professor Hall, there is a stalking-horse element to the debate on medical use; but this should not be allowed to influence the argument either way (p 222).

7.30 The Department of Health still detect an element of the stalking-horse. However they acknowledge and support “the genuine concern of some people to find medicinal products for intractable conditions” (Q 176).

CHAPTER 8 OPINION OF THE COMMITTEE

Medical use of cannabis: recommendations

8.1 We recognise that, in all the evidence we have received, there is not enough rigorous scientific evidence to prove conclusively that cannabis itself has, or indeed has not, medical value of any kind.

8.2 Nevertheless we have received enough anecdotal evidence (see above, paragraphs 5.4, 20–22, 27–30) to convince us that cannabis almost certainly does have genuine medical applications, especially in treating the painful muscular spasms and other symptoms of MS and in the control of other forms of pain.

8.3 **We therefore recommend that clinical trials of cannabis for the treatment of MS and chronic pain should be mounted as a matter of urgency.** We warmly welcome the fact that, in the course of our inquiry, both Dr Geoffrey Guy of GW Pharmaceuticals, and the Royal Pharmaceutical Society's working group under Sir William Asscher, have set off down this route (paragraphs 5.44–48). We welcome the Asscher group's intention to compare the effects of a standardised preparation of natural cannabis with those of the one synthetic cannabinoid already available, dronabinol, on the basis of the same dose level of THC.

8.4 Although neither Dr Guy nor the Asscher group contemplate trials of smoked cannabis, we agree with the Chief Executive of the MRC that such a trial should not be ruled out (paragraph 5.57). However we recognise the dangers of smoking, and we do not envisage smoking being used to administer any medicine eventually licensed. For this reason **we recommend that research be promoted into alternative modes of administration (e.g. inhalation, sub-lingual, rectal) which would retain the benefit of rapid absorption offered by smoking, without the adverse effects.**

8.5 The Government have said repeatedly that, if sufficient evidence in favour of cannabis as a medicine were produced for the MCA to be prepared to license it, they would amend the Misuse of Drugs Regulations so as to permit it to be prescribed. The problem with this policy is that it will take several years at least for this to happen. The Asscher group's trials are not expected to be complete before mid-2001, and will lead only to "proof of principle", leaving others to proceed with any pharmaceutical development. Dr Guy does not expect to receive a product licence in under five years. In the mean time, 85,000 people in this country will continue to suffer the very unpleasant symptoms of MS. Only a small proportion of these are known to have tried cannabis illegally; but of these, significant numbers report great relief of their symptoms. We do not believe that this position is satisfactory.

8.6 **We therefore recommend that the Government should take steps to transfer cannabis and cannabis resin from Schedule 1 to the Misuse of Drugs Regulations to Schedule 2 (see Box 3), so as to allow doctors to prescribe an appropriate preparation of cannabis, albeit as an unlicensed medicine and on the named-patient basis (see Box 6), and to allow doctors and pharmacists to supply the drug prescribed.** This would also, incidentally, allow research without a special licence from the Home Office (see Box 8).

8.7 It is argued in some quarters that some of those who campaign for medical use see it as a stalking-horse for the legalisation of recreational use (paragraphs 7.28–30). We do not see this as a reason to resist medical use if, as we believe, it is justified by the evidence. We prefer the argument recently advanced by Austin Mitchell MP in the House of Commons (14 January 1998, col. 317): at present, people who use cannabis for medical reasons are caught in the front line of the war against drug abuse. This makes criminals of people whose intentions are innocent, it adds to the burden on enforcement agencies, and it brings the law into disrepute. Legalising medical use on prescription, in the way that we recommend, would create a clear separation between medical and recreational use, under control of the health care professions. We believe it would in fact make the line against recreational use easier to hold.

8.8 Before moving cannabis out of Schedule 1, the Government are required by law to consult the Advisory Council on the Misuse of Drugs. **We recommend that they do so at once, and respond to this report only after receiving and considering the advice of the Council.** We recognise that this may take longer than the time normally allowed for such responses.

Medical use of cannabinoids: recommendations

8.9 Unlike cannabis itself, the cannabinoid THC (dronabinol) and its analogue nabilone are already accepted by the Government as having medical value (paragraphs 5.11–17)—producing the anomaly that, while cannabis itself is banned as a psychoactive drug, THC, the principal substance which makes it psychoactive, is in legitimate medical use. Some of our witnesses are prepared (paragraph 5.50) to contemplate wider medical use of the cannabinoids, but not of cannabis itself. We disagree, since some users of both find cannabis itself more effective (paragraph 5.51). We do, however, welcome the inclusion of THC in the trials proposed by the Asscher group, in like-for-like comparison with cannabis itself.

8.10 Dronabinol (THC), though not licensed in this country, has already been moved to Schedule 2 to the Misuse of Drugs Regulations, and nabilone is a licensed medicine and not a controlled drug; so no Government action is required in either case to permit clinical trials or indeed prescription. All cannabinoids other than THC remain in Schedule 1, and transferring them would require agreement through the WHO under the 1971 Convention. We do not regard this as a priority, since we are not persuaded that any other cannabinoid has a convincing medical use; but we recommend that **the Government should raise the matter of rescheduling the remaining cannabinoids with the WHO in due course**, in order to facilitate research.

Why change the law?

8.11 Our principal reason for recommending that the law be changed, to make legal the use of cannabis for medical purposes, is compassionate. Illegal medical use of cannabis is quite widespread (paragraphs 5.2–3); it is sometimes connived at and even in some cases encouraged by health professionals (paragraph 5.6); and yet at present it exposes patients and in some cases their carers to all the distress of criminal proceedings, with the possibility of serious penalties. We acknowledge that, if our recommendation were implemented, the United Kingdom would be moving out of step with many other countries; we consider that the Government should not be afraid to give a lead in this matter in a responsible way.

8.12 As a secondary reason, we would observe that the law in this area appears to be being enforced inconsistently, and in some cases with a very light hand (paragraphs 7.2–5). Some cases are not brought to court; where users of cannabis for medical purposes have been prosecuted, the sentence has sometimes been light; and there have even been cases where juries have refused to convict. The Minister told us that he was content to leave this as a matter for the discretion of the prosecuting authorities and the courts (QQ 668–673). That is a constitutionally proper position for a Minister; but it is not the right position for Parliament. If statute law is not enforced, Parliament is brought into disrepute; either enforcement must be tightened up, or the law must be changed. In this case, we recommend the latter.

8.13 A further subsidiary advantage of transfer from Schedule 1 to Schedule 2 would be the encouragement which this would give to research (paragraphs 7.18–26). There are exciting research opportunities in this field (see Chapter 3), which (on the basis of the number of grants by the MRC and the Wellcome Trust, and the number of Home Office research licences—paragraph 5.39 and Box 8) are not being fully taken up in this country, despite the excellence of British biomedical science. We are satisfied that the Home Office are not being deliberately obstructive; and we are glad that they have already taken up our proposal for a meeting between the research community and those responsible for the research licensing regime (paragraph 7.26). But, now that research in this field has taken off, and the existence of important medical applications is (in our view) well established, it is not appropriate for research to continue to be subject to this extra layer of administration. Transfer to Schedule 2 would also go some way to removing the stigma which

many of our witnesses believe hangs over research in this field, deterring researchers, funding bodies, pharmaceutical companies and local ethics committees alike from involvement in research which might turn out to be of great importance.

8.14 As the Minister pointed out to us, a doctor who prescribed cannabis on these terms, in the absence of a product licensed by the MCA for the relevant indication, would take on himself full responsibility for the consequences (Q 679). This is true. However we have received evidence from doctors who are currently prescribing nabilone on an unlicensed basis (Notcutt Q 405). We believe that the overwhelming majority of members of the medical profession can be trusted not to be reckless in this matter, and that the professional regulatory bodies will deal effectively with any who are.

8.15 The Minister also observed that, in some cases, someone charged with a cannabis offence may claim medical use as a bogus defence or plea in mitigation (Q 674). We do not doubt that this happens at present; and, in the case of some people, it may be hard to tell where recreational use stops and medical use begins (paragraph 5.5). Rescheduling so as to permit prescription would in fact make this problem easier to deal with: rather than having to investigate individual medical histories, as at present, the authorities would simply ask to see the prescription.

8.16 As with any medicine, there are some groups of patients for whom cannabis-based medicines will not be appropriate. On the evidence before us, cannabis-based medicines should not be prescribed for persons with, or predisposed towards, schizophrenic illness (paragraph 4.12) or cardiovascular conditions (paragraph 4.4); nor, pending further research, should they be prescribed for pregnant women (paragraphs 4.15–16). As with many medicines, users should be warned of possible effects on driving ability (paragraphs 4.6–9) and cognitive function (paragraph 4.13). As with any potentially addictive medicine, the risk of addiction (paragraphs 4.23–33) should be weighed up when deciding whether to prescribe, and the user should be warned. **Therefore, if doctors are permitted to prescribe cannabis on an unlicensed basis, the medical professional bodies should provide firm guidance on how to do so responsibly** (paragraph 7.17).

8.17 As with any medicine which is open to abuse, **safeguards must be put in place by the professional regulatory bodies to prevent diversion to improper purposes** (paragraph 7.27). These might include a system of declarations to be signed by the doctor and the patient.

Recreational use

8.18 It is believed in some quarters that the current absolute prohibition on the recreational use of cannabis and its derivatives is not justified by the adverse consequences for the user and the public. On the evidence before us, we disagree. On the contrary, we endorse the Government's statement in *Tackling Drugs*: "The more evidence becomes available about the risks of...cannabis,...the more discredited the notion that [it is] harmless" (paragraph 6.16).

8.19 The harms must not be overstated: cannabis is neither poisonous (paragraph 4.3), nor highly addictive, and we do not believe that it can cause schizophrenia in a previously well user with no predisposition to develop the disease. However, we are satisfied that:

- It is intoxicating, enough to impair the ability to carry out safety-critical tasks (such as flying, driving or operating machinery) for several hours after taking (paragraphs 4.6–9);
- It can have adverse psychic effects ranging from temporary distress, through transient psychosis, to the exacerbation of pre-existing mental illness (paragraphs 4.10–12);
- Regular use can lead to psychological dependence (paragraphs 4.23–33); and, in some dependent individuals (perhaps 5–10 per cent of regular users), regular heavy use can produce a state of near continuous intoxication, making normal life impossible;
- Withdrawal may occasionally involve unpleasant symptoms (paragraphs 4.23–25);

- Cannabis impairs cognitive function during use (paragraph 4.6);
- It increases the heart rate and lowers the blood pressure, carrying risks to people with cardiovascular conditions, especially first-time users who have not developed tolerance to this effect (paragraph 4.4).

8.20 Moreover, it is possible, though not proved, that the effects of cannabis on driving etc. may last longer than a few hours after taking (paragraph 4.7); that the damage to cognitive function may endure after withdrawal (paragraph 4.13); and that cannabis has adverse effects on the immune system (paragraph 5.16) and on fertility and reproduction (paragraphs 4.15–16).

8.21 In addition, smoking cannabis carries similar risks of respiratory disorders to smoking tobacco. It is also possible, though not proved, that exposure to cannabis smoke increases the risk of cancers of the mouth, throat and lung (paragraphs 4.17–18).

8.22 Therefore, **on the basis of the scientific evidence which we have collected, we recommend that cannabis and its derivatives should continue to be controlled drugs.**

Summary of recommendations

8.23

- (i) Clinical trials of cannabis for the treatment of MS and chronic pain should be mounted as a matter of urgency (paragraph 8.3).
- (ii) Research should be promoted into alternative modes of administration (e.g. inhalation, sub-lingual, rectal) which would retain the benefit of rapid absorption offered by smoking, without the adverse effects (paragraph 8.4).
- (iii) The Government should take steps to transfer cannabis and cannabis resin from Schedule 1 to the Misuse of Drugs Regulations to Schedule 2, so as to allow doctors to prescribe an appropriate preparation of cannabis, albeit as an unlicensed medicine and on the named-patient basis, and to allow doctors and pharmacists to supply the drug prescribed (paragraph 8.6).
- (iv) The Government should consult the Advisory Council on the Misuse of Drugs on this matter at once, and respond to this report only after receiving and considering their advice (paragraph 8.8).
- (v) The Government should raise the question of rescheduling the remaining cannabinoids with the WHO in due course (paragraph 8.10).
- (vi) If doctors are permitted to prescribe cannabis on an unlicensed basis, the medical professional bodies should provide firm guidance on how to do so responsibly (paragraph 8.16); and safeguards must be put in place by the professional regulatory bodies to prevent diversion to improper purposes (paragraph 8.17).
- (vii) Cannabis and its derivatives should continue to be controlled drugs (paragraph 8.22).

APPENDIX 1

Members of the Sub-Committee which conducted the enquiry

- * Lord Butterfield
- * Lord Butterworth
- Lord Carmichael of Kelvingrove
- Lord Dixon-Smith
- Lord Kirkwood
- * Lord Nathan
- Lord Perry of Walton (Chairman)
- Lord Porter of Luddenham
- * Lord Rea
- Lord Soulsby of Swaffham Prior
- * Lord Walton of Detchant
- Lord Winston

- * *Co-opted members*

The Sub-Committee appointed as its Specialist Adviser:

Professor Leslie Iversen FRS, Visiting Professor of Pharmacology, University of Oxford

APPENDIX 2

Witnesses

The following witnesses gave evidence. Those marked * gave oral evidence. Those marked ** gave written evidence which is not printed, but is available for inspection at the House of Lords Record Office (0171-219 5316):

- Academy of Medical Sciences (with Royal Society)
- * Advisory Council on Misuse of Drugs
- * Alliance for Cannabis Therapeutics
- ** Anonymous
- * Professor Heather Ashton
- Association of Chief Police Officers
- Dr Anthony Blowers, Surrey's Drug Action Team
- Mary Brett, Dr Challoner's Grammar School (Boys), Amersham
- * British Medical Association
- ** J Brown
- Christian Institute
- ** S Cooke
- David Copestake
- Dr Angela Coutts, University of Aberdeen
- Department of Complementary Medicine, University of Exeter
- ** R Creasey
- ** P Davidson
- ** M Davies
- ** S Day
- * Department of Health
- * Dutch National Institute of Public Health and the Environment
- Evangelical Coalition on Drugs Executive Committee
- ** C Fell
- Forensic Science Service
- ** L Gibson
- Professor Keith Green, Medical College of Georgia, USA
- * Dr Geoffrey Guy
- * Professor Wayne Hall, Executive Director, National Drug and Alcohol Research Centre, Australia
- Professor John Henry, Imperial College School of Medicine (on behalf of Royal College of Pathologists)
- * Dr Anita Holdcroft, Imperial College School of Medicine
- * Home Office
- ** M Humphreys
- Independent Drug Monitoring Unit
- Institute for the Study of Drug Dependence
- International Drug Strategy Institute
- Edward H Jurith
- Dr David Kendall, University of Nottingham Medical School
- * Dr David Lambert
- ** D Lewis
- London Medical Marijuana Support Group
- * Medical Research Council
- * Medicines Control Agency
- Dr Tod H Mikuriya
- * Austin Mitchell MP
- * Mr Neil Montgomery
- * Multiple Sclerosis Society
- * National Addiction Centre
- National Drug Prevention Alliance
- NHS National Teratology Information Service
- * Dr William Notcutt
- Professor David Nutt, University of Bristol

-
- * Dr Roger Pertwee
 - ** A Phillipson
 - ** P Rigby
 - * Dr Philip Robson
 - ** E Rorison
 - Royal College of General Practitioners
 - Royal College of Pathologists
 - Royal College of Psychiatrists
 - * Royal Pharmaceutical Society of Great Britain
 - Royal Society
 - ** J Sayers
 - Dr Fred Schon, Mayday Hospital Croydon and St George's Hospital
 - ** Dr P Shaw
 - ** Councillor C Simpson, Aberystwyth
 - ** L Standen
 - Dr Colin Stewart, Dundee Limb Fitting Centre
 - ** G Vincent
 - Young Christian Democrats

APPENDIX 3

Notes on Conference "Marihuana and Medicine" at New York University Medical Center, New York, 20-21 March 1998

by Professor Leslie Iversen FRS, Specialist Adviser

1. The conference, organised by Professor G. Nahas and colleagues, gave an overview of the current position in the USA. A topical issue there is whether smoked marijuana should be permitted for medical use, since oral formulations of tetrahydrocannabinol (THC) and nabilone are already available medically.
2. M. Huestis (National Institute on Drug Abuse) reviewed new information on the **disposition and metabolism of cannabis** in human subjects, using sensitive analytical techniques to measure THC and some of the major metabolites. Because a substantial proportion of the absorbed THC is sequestered in fat tissues, the half life of the drug in blood is > 4 days and the half life of the major urinary metabolite 11-carboxylic acid THC is > 30 hours. By measuring the ratio of unchanged THC to this metabolite in samples of blood or urine it may be possible to calculate when the last dose of THC was taken—information that could be of importance forensically. An unexpected finding was the large variability between subjects in the amount of THC absorbed by smoking a standard marijuana cigarette under laboratory conditions; even though the number and frequency of puffs was controlled there was a 3-fold range. For the same subject tested on different occasions there was also a considerable variability in the amount of THC absorbed (17 per cent on average).
3. M. El Sohly (University of Mississippi) described the development of a **rectal suppository** formulation for delivery of THC in the form of a "pro-drug" (the hemisuccinate ester) dissolved in a lipid base. Absorption of THC increased in a dose-dependent manner and was prolonged (THC was measurable in blood for up to 8 hours). Because this route of absorption avoids first pass metabolism in the liver, the amount of THC absorbed into circulation was more than twice as great as after oral dosage. Unfortunately there was a high variability between subjects in the amount of THC absorbed (about 3-fold). The advantages of this route of administration seem clear, but it was thought unlikely to be popular in the United States where suppository formulations have never been widely accepted.
4. B. Thomas (Research Triangle Institute) reviewed the operation of his laboratory which supplies **standard marijuana cigarettes** to the 8 individual glaucoma patients licensed in the US to receive this medication, and to research groups in the US and elsewhere. By using standard growing conditions (at the University of Mississippi) and different strains of cannabis plant they are able to generate marijuana cigarettes of consistent quality and standard THC content (standard = 1.8 per cent THC; strong = 4.0 per cent THC) free of microbial or insect contamination. Placebo cigarettes are prepared using leaf material extracted with alcohol to remove THC.
5. Roger Pertwee (University of Aberdeen) reviewed current knowledge of the two **cannabinoid receptors** CB1 (found in the brain and some peripheral organs) and CB2 (peripheral only). The presence of CB2 receptors on cells in the immune system has prompted some pharmaceutical companies to become interested in this as a possible target for the discovery of novel immune-suppressant or anti-inflammatory drugs. The French company Sanofi and the Canadian company Merck-Frosst have reported novel synthetic antagonists/agonists acting selectively at these sites. The availability of novel synthetic antagonists acting at the CB1 receptors (eg SR141716A (Sanofi), LY 320135 (Eli Lilly)) has provided valuable new research tools. New drugs are also being designed based on the structure of the endogenous cannabinoid anandamide.
6. R. Mechoulam (Hebrew University, Israel) described his identification of Δ^9 -THC as the principal psychoactive compound in cannabis extracts, and his subsequent discovery of **anandamide** as the naturally occurring cannabis-like compound in the brain. Other naturally occurring fatty acid derivatives also interact with cannabis receptors, and one of these, 2-arachidonylglycerol, may act selectively at CB2 receptors.

7. E. Gardner (Albert Einstein College of Medicine, New York) described studies of the interaction of THC with **reward pathways** in rat brain. He confirmed earlier work from an Italian laboratory (Tanda et al, 1997, *Science*, 276:2048-2050) that administration of THC (0.5mg/kg) to rats caused an increase in dopamine release in the nucleus accumbens region of the brain and, furthermore, that this release could be blocked by co-administration of the drug naloxone, which blocks opiate receptors in the brain. He also found that THC sensitised rats to the rewarding effects of intracranial self-stimulation and that this effect was also blocked by naloxone. These results are potentially important as they indicate that THC stimulates dopamine pathways in the brain known to be activated by various addictive drugs—nicotine, amphetamine, heroin and cocaine. The blocking effects of naloxone suggest that THC may exert at least part of its rewarding effects indirectly by promoting a release of opiate-like chemicals in the brain.
8. D. Tashkin (University of California Los Angeles) surveyed the **effects on the lung** of long-term marijuana use. He conducted large scale studies in the 1980s in heavy marijuana smokers and compared them with subjects who smoked tobacco. Marijuana smokers showed some bronchial symptoms (cough, wheeze and bronchitis), but there was no evidence for any significant reduction in overall respiratory function. When data were collected annually for a further 8 years, the marijuana smokers did not show the age-related decline in respiratory function seen in tobacco smokers. Nevertheless, there was concern about the longer-term effects of marijuana smoking. Examination of the lining of the airways revealed inflammatory changes in chronic marijuana smokers, with an increase in the number of mucus-secreting cells and sometimes what appeared to be pre-cancerous alterations in cells lining the lungs. Examination of lung biopsy specimens showed an increased expression of certain genes that are markers of lung tumours. In addition the immune defence system appears to be depressed in the lungs of marijuana smokers. The defending white cells (macrophages), although present in increased numbers, had a decreased ability to kill bacteria or fungi and produced reduced amounts of nitric oxide and cytokines, the normal defence chemicals. Suppression of immune system function may be related to a direct effect of cannabis on receptors on the macrophages and other immune system cells. Although there was no evidence for increases in lung cancers in marijuana smokers, there were some reports of increases in cancers of mouth and throat. The reduction in immune system function could make marijuana smokers especially vulnerable to lung infections.
9. K. Coe (formerly at Pfizer Research) and L. Lemberger (formerly at Eli Lilly Research) gave historical reviews of the **development of novel drugs** for the treatment of pain and prevention of nausea based on cannabinoid chemical structures. A project at Pfizer in the 1970s led to the discovery of the synthetic compound levonantradol and the related compound CP-55,940. These compounds had a much greater water solubility than THC and proved to be up to 100 times more potent than morphine in some animal tests of pain. Levonantradol entered pilot scale clinical trials and was effective in suppressing post-operative pain and in preventing nausea and vomiting associated with cancer chemotherapy. It was evident, however, that the drug did not separate the beneficial clinical effects from intoxicant effects, and the company abandoned the project in 1980. CP-55,940 proved valuable, however, in radioactively labelled form as a probe which led to the identification of the cannabis CB1 receptor in the brain.
10. At Eli Lilly during the same period there was also a hope that the beneficial effects of cannabinoids could be separated from unwanted psychoactivity, and this led to the discovery and development of **nabilone**. Clinical trials established the effectiveness of this drug in the treatment of the nausea and vomiting associated with cancer chemotherapy. Although some patients complained of the drug-induced "high", this appeared milder than that associated with THC. However, although nabilone was approved for medical use by the Food and Drug Administration, the US Drug Enforcement Agency insisted that it be given a "Schedule II" classification [i.e. a compound with some medical use but a high abuse potential, so doctors using it have to keep detailed records]. This led to the company withdrawing from the project and also failing to give any substantial marketing support to the compound. Post-marketing surveillance reports in the UK, where the compound has some limited use, have not shown any danger of abuse.
11. W. Notcutt (Great Yarmouth), a consultant in a pain clinic, reported on the positive effects of nabilone in the **relief of pain** in some of his patients who were suffering from chronic pain and

not responding to other medications. In a total of 55 patients he observed beneficial effects of nabilone (improved sleep, reduced pain) in about one third.

12. K. Green (Medical College of Georgia) and M. Forbes (Columbia University College, NY) discussed the possible use of cannabis in the treatment of **glaucoma**. There are more than 2 million glaucoma patients in the USA alone, and glaucoma is a major cause of blindness. THC or smoked marijuana does cause a marked fall in intraocular pressure in both normal subjects and patients with glaucoma (up to 45 per cent reduction), but the effect is transient and returns to baseline within 3-4 hours. It is difficult to achieve longer-term control of intraocular pressure as this would require frequent repeat dosing. THC cannot be delivered topically to the eye (the preferred route for anti-glaucoma medications) because of its low water solubility. It is possible that an improved topical delivery formulation, or topical use of a more water soluble synthetic cannabinoid, could be developed in the future. In the USA a small group of patients (8) have individual permission to use smoked marijuana to treat their glaucoma.
13. R. Graller (New Orleans) reviewed the use of cannabis in the treatment of **nausea and vomiting**. Although there have been several controlled clinical trials showing the effectiveness of orally administered THC and nabilone in patients receiving cancer chemotherapy, there are few data on smoked marijuana. In recent years a new class of anti-nausea drugs, the 5-HT₃ antagonists (e.g. ondansetron, granisetron) have radically improved the treatment of nausea and vomiting in cancer patients. He found that a combination of granisetron and the steroid dexamethasone controlled the symptoms in more than 90 per cent of patients. Unlike THC which cannot be given intravenously, granisetron can be given by this route as well as by mouth.
14. G. Francis (McGill University, Montreal) discussed the use of cannabis in the treatment of **multiple sclerosis**. There are few effective treatments for this disease, and more than 250,000 patients in the USA. Some symptoms are particularly poorly controlled by existing medicines, notably tremor, pain and spasticity. There are many anecdotal reports that these symptoms are eased by smoked marijuana, but so far there have been few controlled clinical trials. A currently ongoing study with 600 subjects aims to compare smoked marijuana with a placebo (cigarettes with THC removed). Results available so far suggest that the subjective reports of improvement by patients are not always accompanied by improvement in objective measures of performance.

APPENDIX 4

Notes on the International Cannabinoid Research Society 1998 Symposium on Cannabinoids,
La Grande Motte, France, 23-25 July 1998
by Professor Leslie Iversen FRS, Specialist Adviser

1. The annual meeting of this group of research scientists was held for the first time outside North America and was attended by about 150 scientists, largely from academia. Of the 135 papers presented 73 originated from the United States and 50 from Europe (including 12 from Britain, 5 of which were from Dr Pertwee's group in Aberdeen).

Endogenous cannabinoids

2. A substantial number of papers focused on the naturally occurring cannabinoids in the brain and in peripheral tissues. At least two lipid derivatives are now recognised: anandamide (arachidonyl-ethanolamide) and an arachidonic acid ester, 2-arachidonyl-glycerol (2-AG). The latter substance is as potent as anandamide and is present in much larger quantities than anandamide in the brain. Several papers focused on the biochemical mechanisms involved in the synthesis and degradation of these lipids in the brain, and progress has been made in defining the biochemical mechanisms involved. Attention has also focused on the development of metabolically more stable chemical analogues of anandamide and 2-AG with improved activity in whole animal studies: the naturally occurring compounds are rapidly degraded and are thus not very active *in vivo*. Another lipid, palmitoyl-ethanolamide, may represent the natural activator of CB2 receptors, although there was some disagreement about its pharmacological activity and selectivity.

Cannabinoid receptors

3. Several groups are studying the detailed molecular architecture of the CB1 and CB2 receptors and beginning to identify the precise sites at which the cannabinoids bind to these proteins. Studies of the receptors in *in vitro* model systems have revealed some interesting differences between the effectiveness of various cannabinoids in activating the receptors. In particular Δ^9 -THC appears to act as only a partial agonist at the CB1 receptor (i.e. it cannot elicit a maximum response). Cannabidiol, one of the most abundant plant alkaloids, on the other hand appears to act as an antagonist at the CB1 receptor.
4. The CB1-selective antagonist drug SR141716A and the related CB2-selective antagonist SR144528 from the French pharmaceutical company Sanofi were the subject of many papers, and these compounds have proved to be important new research tools for probing cannabinoid functions. Scientists from Sanofi revealed that they are developing SR141716A for clinical trials, with schizophrenia as their first target (on the rationale that high doses of THC can cause a schizophrenia-like psychosis). A novel CB1 antagonist CP-272871 from Pfizer was described for the first time; it has properties similar to those of SR141716A.
5. The CB2 receptor, located principally on cells in the immune system, has attracted attention from a number of major pharmaceutical companies as a potential target for discovering novel anti-inflammatory or immuno-suppressant drugs. There has been progress in identifying CB2-selective drugs (by Merck Frosst, Glaxo-Wellcome, and Smith Kline Beecham) but so far there is little confidence that this target will prove useful. Dr Nancy Buckley (US National Institutes of Health) described the "CB2 knockout mouse" in which as a result of genetic engineering the CB2 receptor is no longer expressed. These mice seem remarkably normal in their immune cell population and in immune function and have not so far assisted in understanding the role normally played by the CB2 receptors.

Adverse effects

6. D. Tashkin (UCLA) reported that treatment of mice with THC (5 mg/kg four times a week) led to more rapid growth of implanted lung cancer cells and decreased survival. He suggests that THC may suppress immune-mediated eradication of tumour cells.
7. A session sponsored by the US National Institute on Drug Abuse focused on the effects of long-term cannabis use on frontal lobe function in man. A series of studies using imaging, cerebral blood flow and electroencephalographic measurements indicated depressed frontal

lobe function in long-term cannabis users, and there were accompanying subtle deficits in sensory and cognitive processing, the so-called "executive functions" of the brain. There was little evidence that any of these effects persisted after cessation of drug intake.

8. Billy Martin *et al* (Virginia, USA) described an animal model of cannabis dependence. When dogs were treated with high doses of THC for 7-14 days and then challenged with the CB1 antagonist SR141716A clear physical signs of withdrawal became apparent; these included trembling, shaking, restlessness, vomiting and diarrhoea. By using the antagonist challenge model it has become much clearer that physical dependence and withdrawal can occur with THC, at least in animals. Furthermore, de Fonseca *et al* (Madrid) reported that the administration of SR141716A to morphine-dependent animals elicited a behavioural and endocrine syndrome similar to that seen in opiate withdrawal, although considerably milder. Conversely some withdrawal signs could be elicited in cannabinoid-dependent animals when challenged with the opiate receptor antagonist naloxone, suggesting an interaction between the opioid and cannabinoid systems in the brain.

Possible applications of cannabinoids

9. The interaction of opiate and cannabinoid mechanisms was also highlighted by Sandra Welch (Medical College of Virginia, USA) who reported that low doses of THC significantly potentiated the pain-relieving effects of morphine and other opiates in a mouse model of arthritis-like pain. Higher doses of THC were also by themselves fully effective in causing analgesia in this model. She is planning a clinical trial (with the approval of the US Food & Drug Administration) of low doses of THC (dronabinol) in conjunction with self-administered morphine in patients suffering from cancer pain, in the hope that the drug combination may make morphine more effective in such patients.
10. D. Piomelli (San Diego, USA) described powerful analgesic effects of anandamide when injected directly into the rat paw in an inflamed paw model of inflammatory pain. The mechanism appeared to involve both CB1 and CB2 receptors located on sensory nerve fibres in the skin, and when a combination of CB1-selective and CB2-selective compounds was injected there was synergy between them. Experiments using radiolabelled anandamide showed that >90 per cent of the injected dose remained in the paw, and very little entered the brain or spinal cord. These results are highly original and suggest the possibility that cannabinoids can exert pain-relieving actions without having to penetrate into the central nervous system.
11. P. Consroe and R. Musty (University of Arizona, USA) described the results of an anonymous survey of 106 patients with spinal cord injuries who were self-medicating with smoked marijuana. Patients smoked an average of 4 joints a day, 6 days a week and had been doing so for >10 years. More than 90 per cent reported that cannabis helped improve symptoms of muscle spasms of arms or legs, and improved urinary control and function. Around 70 per cent reported pain relief. The results of this survey and a similar one conducted with R. Pertwee in MS patients may help to pinpoint the relevant symptoms to focus on as outcome measures in future clinical trials of cannabis or cannabinoids.
12. D. Pate (University of Kuopio, Finland) described promising results in the reduction of intraocular pressure when a metabolically stable anandamide analogue was applied topically to normal rabbit eye. This effect appeared to involve a local CB1 receptor mechanism as it could be blocked by pretreating the animals with the antagonist SR141716A. In order to deliver the water-insoluble lipid derivative to the eye it was dispersed in an aqueous solution containing a beta-cyclodextrin carrier.

Miscellaneous

13. M. El Sohly (University of Mississippi, USA) summarised results obtained from the analysis of confiscated marijuana samples, a service which has been running since 1980 and which involves the analysis of samples from all regions of the United States. Data from 35,312 samples were available. The potency of marijuana leaf samples (the commonest in US seizures) rose from around 1.5 per cent THC content in 1980 to around 3 per cent in the 1980s and most recently to 3.87 per cent in 1996 and 4.15 per cent in 1997. The THC content of sinsemilla (the female plant flower head) rose from around 6.5 per cent in 1980 to 9.22 per cent (1996) and 11.53 per cent (1997). The increases are thought to be due to improved culture conditions rather than to any genetic improvements. Analysis of samples of cannabis

resin or oil revealed few discernible trends, with figures ranging from 3 per cent to 19 per cent THC content.

14. J. Khodabaks and O. Engelsma (Maripharma, Netherlands) described their development of "The standardised medical grade marihuana plant". Until recently this group has been supplying Dutch pharmacists with medical grade marijuana, but its legal status has recently been questioned. The laboratory cultivates standard cannabis plants selected for a high yield of THC and low content of other cannabinoids; these are cloned by propagating (by cuttings) from female plants. The plants are grown under standard conditions and the female flower heads harvested and vacuum-sealed for storage and then gamma-irradiated to sterilise the preparations. Samples are routinely checked for THC and other cannabinoids and to ensure that they are free of pesticides. The THC content in different batches was highly consistent at 10.7 ± 0.1 per cent (standard deviation). Interestingly, in the light of discussions about the relevance of other cannabinoids in herbal cannabis, cannabidiol and cannabinol were present in only minor amounts (<0.1 per cent) in these samples.

APPENDIX 5

Abbreviations

ACMD	Advisory Council on the Misuse of Drugs
ACT	UK Alliance for Cannabis Therapeutics
AMA	American Medical Association
BMA	British Medical Association
CMO	Chief Medical Officer
CPS	Crown Prosecution Service
DETR	Department of the Environment, Transport and the Regions
DH	Department of Health
HC	House of Commons (<i>Hansard</i>)
HL	House of Lords (<i>Hansard</i>)
FSS	Forensic Science Service
IDMU	Independent Drug Monitoring Unit
ISDD	Institute for the Study of Drug Dependence
LMMSG	London Medical Marijuana Support Group
MCA	Medicines Control Agency
MRC	Medical Research Council
MS	Multiple sclerosis
MSSoc	Multiple Sclerosis Society
NDPA	National Drug Prevention Alliance
NHS	National Health Service
NTIS	NHS National Teratology Information Service
POST	Parliamentary Office of Science and Technology
RCGP	Royal College of General Practitioners
RCPATH	Royal College of Pathologists
RCPsych	Royal College of Psychiatrists
RPharmSoc	Royal Pharmaceutical Society of Great Britain
THC	Tetrahydrocannabinol (Δ^9 -tetrahydrocannabinol unless otherwise specified)
WA	Written Answer (in <i>Hansard</i>)
WHO	World Health Organization
UN	United Nations

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